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Understanding the impact of environmental stress

The effect of childhood abuse on brain structure and stress response systems in psychosis

Ciufolini, Simone

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**UNDERSTANDING THE IMPACT OF ENVIRONMENTAL STRESS:
THE EFFECT OF CHILDHOOD ABUSE ON BRAIN STRUCTURE AND
STRESS RESPONSE SYSTEMS IN PSYCHOSIS**

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**Thesis submitted for the degree of
Doctor of Philosophy**

Institute of Psychiatry, Psychology and Neuroscience

King's College London

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“Few men realize that their life, the very essence of their character, their capabilities and their audacities,
are only the expression of their belief in the safety of the surroundings.
The courage, the composure, the confidence; the emotions and principles;
every great and every insignificant thought belongs not to the individual but to the crowd;
to the crowd that believes blindly in the irresistible force of its institutions and of its moral,
in the power of its police and its opinion. “
Joseph Conrad¹

¹ An outpost of progress.

Abstract

The biological mechanisms through which childhood physical and sexual abuse increase the risk of psychosis are unclear. This thesis investigated the presence of abnormalities in brain structure and in the hypothalamic-pituitary-adrenal (HPA) axis activity in people at their first episode of psychosis (FEP) and controls, with and without a history of childhood abuse.

Structural MRI scans were acquired in 86 FEP patients (49 abuse positive) 64 controls (30 abuse positive). The HPA axis was evaluated in 169 FEP (110 abuse positive) and 133 controls (67 abuse positive). In this population I explored differences in grey matter volume and cortical thickness and cortisol concentrations during the day and at awakening in association with abuse exposure. Finally I correlated cortisol levels with cortical thickness in regions sensitive to abuse.

Childhood abuse was associated with smaller grey matter volume and reduced cortical thickness in frontal and occipital brain regions. I found an interaction between psychosis and abuse in frontal and parietal regions, which had greater grey matter volume and cortical thickness in controls and smaller in FEP exposed to childhood abuse. There was an interaction between psychosis and abuse in the cortisol awakening response (CARg) as FEP exposed to severe childhood abuse showed a blunted CARg while controls exposed to severe abuse had higher CARg. Finally there was a negative correlation between cortisol and cortical thickness: larger thickness in brain frontal and parietal regions sensitive to abuse exposure were correlated with lower cortisol levels during the day in controls but not in FEP.

Childhood abuse has a differential impact on the brain structure as well as the HPA axis activity in FEP and controls. The relationship between cortisol and cortical thickness in regions sensitive to abuse found

only in controls suggests an integration of brain structure and HPA axis activity and possibly an adaptive mechanism to environmental stress.

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“Sino ad allora avevo pensato che ogni libro parlasse delle cose,
umane o divine, che stanno fuori dei libri.
Ora mi avvedevo che non di rado i libri parlano di libri,
Ovvero e' come si parlassero tra di loro”

Umberto Eco²

This thesis will refer solely to technical concepts, rigorous studies and well-substantiated theories and will try to place itself within the scientific debate of my field of study, as every scientific manuscript should aim for. Nonetheless it also has some obligations with the outside world which I would like to honour before going further. First I would like to thank my supervisors Dr. Paola Dazzan, Dr. Valeria Mondelli e Dr. Matthew Kempton for their invaluable support, help and guidance over the years. They proved right Dr Stefania Bonaccorso and a piece of advice she gave me when I wanted to spend a few months at the IoPPN as part of my training in psychiatry more than four years ago and for which I am beholden. I am indebted with all the participants, researchers and the staff of the GAP and EUGEI study who made possible the database I used. I am grateful to my friends and colleagues for having shared with me knowledge as well as productive and unproductive time at the institute, in the pubs nearby and when the fire alarm rang. I am thankful to my friends here in London and in Italy, I do think I do not really need to say why.

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Last Alessandra che e' la mia Vava (*ma femme, ma joie et mon allegresse*).

² Il nome della rosa (“Until then I had thought each book spoke of the things, human or divine, that lie outside books. Now I realized that not infrequently books speak of books: it is as if they spoke among themselves.” The name of the rose).

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Abbreviations

ANOVA - Analysis Of Variance

ANCOVA – Analysis Of CoVariance

CARg -Cortisol Awakening Response with respect to ground

CARi -Cortisol Awakening Response with respect to increase

CECA - Childhood Experience of Care and Abuse

CECA-Q - Childhood Experience of Care and Abuse Questionnaire

DARTEL - Diffeomorphic Anatomical Registration Through Exponential Lie Algebra

DOSS - Different Offset Same Slope

DODS - Different Offset Different Slope

DUP Duration of Untreated Psychosis

FWE - Family wise error

FWHM - Full Width at Half Maximum

GLM - General Linear Model

HPA - Hypothalamic Pituitary Adrenal

MPRAGE - Magnetization-Prepared Rapid Gradient-Echo

MR – Mineralocorticoid Receptor

GR – Glucocorticoid Receptor

MRI – Magnetic Imaging

OPCRIT – Operational Criteria Checklist For Psychotic Illness

PANSS - Positive and Negative Syndrome Scale

ROI - Region Of Interest

SLAM – South London And Maudsley

SPM - Statistical Parametric Mapping

SVC - Small Volume Correction

VBM -Voxel Based morphometry

TIV - Total Intracranial Volumes

Overview of the thesis

The scope of this project is to delineate how physical and sexual abuse increases the risk of psychosis. This is examined by exploring the presence of abnormalities in the brain structure and activity of the hypothalamic-pituitary-adrenal (HPA) axis in people at their first episode of psychosis and in healthy controls, with and without a personal history of childhood abuse. The exploration of the impact of abuse on these two biological systems runs as parallel lines of investigation for most of the manuscript and these two lines are integrated to describe the biological process that may contribute to the onset of psychosis in subjects who suffered childhood physical and sexual abuse. The thesis is divided into four chapters³ describing either the investigation of brain structure or the HPA axis or the integration of both. This lends itself to two ways of reading the manuscript. The first one is to follow the sections and the chapters in the order they are presented. The second one is a more thematic way of approaching the project: irrespective of the order of the chapters, the reader can focus on one investigation at a time, either on the effect of abuse on the brain or on the HPA axis, and then on exploring whether the alterations in the two biological systems have relationships with each other. To help guide the reader, Table 1 indicates which chapters pertain to the exploration of abuse and brain structure, the HPA axis or these two systems together. Whichever way they would choose I hope the reading would be informative and enjoyable.

³ 1. Introduction and Rationale of the study; 2. Methods; 3. Results; 4. Discussion and Conclusion.

Table1: Structure of the thesis	Cortisol	Neuroimaging	Both
1 Introduction and Rationale of the study⁴			
1.1. What is left to know? Why to investigate environmental risk factors in psychiatry?			✓
1.2. What is psychosis?			✓
1.3. What is stress? What is trauma?			✓
1.4. Cortisol	✓		
1.5. Brain structure		✓	
1.6 Rationale for the study			✓
2 Methods			
2.1 Research Design			✓
2.2 Structural MRI Methodology		✓	
2.3 Hypothalamic-pituitary-adrenal (HPA) axis function methodology	✓		
2.4 Interaction between structural MRI and Hypothalamic-pituitary-adrenal (HPA) axis function methodology			✓
3 Results			
3.1 Socio-demographic Characteristics, Abuse Exposure, and Clinical Evaluation			✓
3.2 Results of Structural MRI		✓	
3.3 Results of HPA axis activity	✓		
3.4 Correlation between brain structure and HPA axis			✓

⁴ The three shades of blue associated to the sub-chapters that reference Cortisol, Neuroimaging or both of them, are coherently maintained in the explanatory tables and images along all structure of this work.

activity			
4 Discussion and Conclusion			
4.1 Overview Socio-demographic Characteristics, Abuse Exposure, and Clinical features in the entire samples			✓
4.2 Childhood abuse and brain structure		✓	
4.3 HPA axis activity and childhood abuse	✓		
4.4 Brain structure, HPA axis activity and childhood abuse			✓
4.5 Limitations			✓
4.6 Conclusion			✓

1 Introduction and Rationale of the study

There are these two young fish swimming along, and they happen to meet
an older fish swimming the other way, who nods at them and says,
“Morning, boys, how's the water?” And the two young fish swim on for a
bit, and then eventually one of them looks over at the other and goes,
“What the hell is water?”

David Foster Wallace⁵

⁵ This is water, Little, Brown and Company 2009

1.1 What is left to know? Why investigate environmental risk factors in psychiatry

Classic twin studies consistently demonstrate a high level of heritability of schizophrenia, bipolar disorder and major depression as well as high degree of genetic overlap across disorders, implying a common aetiology (Cardno et al. 1999; McGuffin et al. 1996; Kieseppä et al. 2004; Rasic et al. 2014). Whilst the liability to severe mental illness seems to be defined mainly by the degree of biological relatedness with individuals showing this phenotype, the delineation of direct paths from gene to disease has proven elusive (Uher 2014). In recent years a more nuanced picture has been defined, as family and population studies on one hand and molecular genetic data on the other have contributed to delineating the role of genetic and environmental influences on schizophrenia, severe bipolar disorder and major depression.

Since the seminal study of Francis Galton in 1875, research has devised progressively more sophisticated methods to gauge the “relative powers of nature” (genetic disposition) “and nurture” (environmental exposure) (Galton, 2012). The heritability of a phenotype is usually assessed by examining the resemblance of the phenotype itself across relatives and estimating how much of this variance is due to genetic differences in a given group of individuals. Monozygotic and dizygotic twins, siblings born at the same time from the same parents and sharing up to 100% and 50% of their genes respectively, constitute a unique opportunity to tease apart genetic predisposition from the role of the environment in the aetiology of disease (van Dongen, Slagboom, Draisma, Martin, & Boomsma, 2012). Twin studies have therefore been used to quantify the contribution of genetic factors in schizophrenia, bipolar disorder and major depression, consistently suggesting that high liability to these mental illnesses is owing to genetic factors, with schizophrenia and bipolar disorder varying between 70% and 80% and major depression in

the range of 48% - 75% (Cardno et al. 1999; McGuffin et al. 1996; Kieseppä et al. 2004; Lee et al. 2013; Uher 2014). It has been challenging to translate these consistent estimates into the discovery of significant loci and similarly, the replication of previous published associations has proven elusive (Uher 2009; Lee et al. 2013; Uher 2014). Thus the picture is far from being conclusive, as loci with genome-wide significance are surprisingly sparse and have reduced reproducibility, making the characterization of the biological mechanisms of psychosis seems still remote (Cardno et al. 1999; McGuffin et al. 1996; Kieseppä et al. 2004; Lee et al. 2013; Uher 2014). Importantly a recent study from the Schizophrenia Working Group of the Psychiatric Genomics Consortium evaluated a sample of 36,989 cases and 113,075 controls and has found 108, 83 new and 23, loci linked with schizophrenia, supporting the idea of schizophrenia as a disease with a solid base of risk SNPs with individually small effects (Ripke et al., 2014). However, the evidence for other disorders is not so advanced: the Psychosis Endophenotypes International Consortium and the Wellcome Trust Case-Control Consortium 2 (2014) found no association for individual selected single-nucleotide polymorphisms SNPs in schizophrenia, schizoaffective and psychotic bipolar disorder (Psychosis Endophenotypes International Consortium; Wellcome Trust Case-Control Consortium 2, Bramon E, Pirinen M, Strange A, Lin K, Freeman C, Bellenguez C, Su Z, Band G, Pearson R, Vukcevic D, Langford C, Deloukas P, Hunt S, Gray E, Dronov S, Potter SC, 2014). A similar uncertainty is present in the case of affective disorders (Uher 2009; Consortium 2013; Endophenotypes et al. 2014). Recently the Wellcome Trust Case–Control Consortium GWAS found no association for bipolar affective disorder and the Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, in a mega-analysis of genome-wide association studies for major depressive disorder, were “unable to find robust and replicable findings” (Uher 2009; Consortium 2013; Endophenotypes et al. 2014). When loci are found they explain only a small amount of variance (K. W. Lee, Woon, Teo, & Sim, 2012). As a consequence, there is a large “heritability gap” between twin and molecular data; the aggregate heritability explained by the known risk genes is estimated around 22% for schizophrenia(58% heritability gap), around 25% for bipolar disorder (50% heritability gap), and around 20% for depression (16% heritability gap for depression and 28% for severe depression) (R Uher, 2009).

In the last decade a new and more dynamic view of the relation between genome and phenotype has emerged, which may help reconcile these contradictory findings. A phenotype is now thought to be the multifaceted outcome of the presence (or absence) of a specific allele as well as gene-gene interactions, and their interaction with environmental factors (Uher 2009; van Os et al. 2010; Lee et al. 2012). Animal studies as well as family data have indeed revealed that the penetrance of one gene on traits and behaviours is often dependent on the presence of one or more ‘modifier’ gene able to enhance or reduce its impact (Uher 2009; Lee et al. 2012). Therefore, the estimation of genetic risk does not always equate to the sum of the contribution of each single gene, as is often the case in heritability estimates from traditional genetic studies (Uher 2009; Lee et al. 2012). Creating an ensemble of loci with a weighted sum of trait-associated alleles to test their relation with the phenotype and prove their predictive value (polygenic score) has been a successful strategy to explore shared genetic aetiology among traits (Dudbridge, 2013). Evidence is mounting that the use of polygenic score is a viable solution to identify constellations of genes that together are responsible for important traits in both schizophrenia and bipolar disorder (Purcell et al., 2009). Likewise, the environment has a more significant impact on genetically more sensitive individuals (gene-environment interaction) and dynamically moderates the gene expression (epigenetic changes) (Pidsley and Mill 2011; van Os 2014). Unfortunately the importance to the development of severe mental illnesses of the environmental factors able influence the phenotype (e.g. poverty, migration or abuse) is not properly evaluated in traditional genetic studies (Plomin et al. 2001; Uher 2009). Indeed they tend to allocate the contribution of the environmental factors either to the additive genetic component or to the non-shared environment inflating the final heritability estimate (Plomin et al. 2001; Uher 2009). This issue is magnified for idiosyncratic experiences or rare events with a more pronounced effect at the individual level rather than the group or familiar level, as they tend to be misallocated, thus inflating the differences among siblings (Plomin et al. 2001; Uher 2009). This is often the case for abuse, a well established risk factors for severe mental illness, which is seldom evaluated appropriately in a twin or classical genetic study, as it is often added to the heritability estimate (Plomin

et al., 2001). The potentialities of an approach that could estimate the impact of the environment on the genome was made transparent by Caspi et al. (2003) in their seminal gene-environment interaction study. They showed how the functional polymorphism in the promoter region of the serotonin transporter (5-HTT) moderates the influence of stressful life events on depression, with individuals bearing one of two copies of the short alleles being more susceptible to the effects of a negative environment than people with the longer allele (Caspi et al., 2003). Similarly, epigenetic changes have shown to be involved in the alterations in the brain structure of individuals with schizophrenia and bipolar disorder (Pidsley and Mill 2011). These approaches have the potentiality to explain a greater amount of variance than traditional genetic studies in severe mental health illnesses and may provide new insight into this pathophysiology (Purcell et al. 2009; Pidsley and Mill 2011; van Os 2014). With the increase in the availability of different analysis methodologies where the selection of a-priori SNPs or alleles of interest is so important, inevitably, reliable results and convincing interpretations hinge more and more on an accurate identification of the biological pathways behind psychosis (J. E. A. van Os, 2014). The challenge of conducting large population studies has led to uncertainty about the reproducibility and the reliability of some gene-environment interaction findings, as such studies may be underpowered to detect interactions (Hunter, 2005). One possibility for circumnavigating these limitations is to gain a better understanding of the biological mechanisms present in psychosis to devise hypothesis-driven genetic studies (Hunter 2005; van Os 2014).

In recent years physical and sexual abuse, a specific type of childhood adversity, has been established along with urbanicity, migration and consumption of recreational drugs as one of the main environmental risk factors for psychosis (Henquet et al. 2005; Morgan et al. 2010; Varese et al. 2012). Unfortunately, an understanding of the biological mechanisms explaining how these environmental risk factors lead to psychosis is lacking (Henquet et al. 2005; Morgan et al. 2010; Varese et al. 2012). As physical and sexual abuse are relatively rare occurrences, studies have often grouped them with other types of childhood adversities (e.g. psychological abuse, physical neglect) to increase sample size and consequently

statistical power. Different types of abnormalities and severity can have different impacts on the individuals and impinge on different biological mechanisms; furthermore, they are thought to interact with each other in a non-linear fashion, thus further increasing the difference in outcome with individuals with just one traumatic experience (Heim, Shugart, Craighead, & Nemeroff, 2010). Grouping together individuals with dissimilar levels of exposure to abuse has led to the inevitable introduction of noise, leaving unclear the relationships between each childhood adversity and the biological mechanisms involved (Morgan et al. 2010; Varese et al. 2012). The use of samples homogeneous in terms of abuse severity could provide a possibility to study the biological mechanisms elicited by abuse more clearly. In this study I investigate the effect of physical and sexual abuse during childhood on the brain structure and stress response in a sample of adult individuals with and without exposure to these experiences. Furthermore, I consider whether their effects differ in adults with and without psychosis, to explore whether they are involved in the biological processes behind the psychotic disease. Finally, to better validate the impact of these types of abuse, I look at whether the abnormalities in these two biological systems are associated in psychosis.

1.2 What is psychosis?

The term psychosis defines a mental state characterised by grossly impaired reality testing. Individuals in a psychotic state infer incorrectly about reality, are incapable of determining the accuracy of their thoughts and perceptions and are unable to change their minds even if presented with contrary evidence (Kalan and Sadock 2000). Psychosis is also accompanied by severe impairment of social and personal functioning, characterised by social withdrawal and inability to perform activities of daily life and occupational roles. Psychosis is not a diagnosis *per se* and is not defined in the International Classification of Diseases (ICD-10) (World Health Organization, 1992) or in the DSM-V (American Psychiatric Association, 2013a) and rather comprises a symptom or set of symptoms that may have several causes. It is, in fact, an umbrella term for a group of heterogeneous disorders, including some that have been previously considered as distinct entities, such as schizophrenia, schizophreniform disorder, delusional disorder, schizoaffective disorder and affective psychoses (i.e. bipolar or depressive disorder with psychotic symptoms).

The identification of psychosis is possible in presence of delusions, hallucinations and formal thought disorder. Delusions represent false, unshakable personal ideas or beliefs about the external reality, unshared within the community to which the individual belongs and firmly held despite obvious contradictory proof or evidence. Hallucinations are false perceptions in the absence of a real external stimulus but which are perceived as having the same quality as real perceptions: they are not subject to conscious manipulation and can occur in any sensory modality. Hallucinations may include simple perceptions (such as light, colours, tastes and smells) or more complex experiences such as seeing and interacting with fully formed animals and people, hearing voices and composite tactile sensations. Formal thought disorder is a disturbance in the form of thoughts where the thought process is characterised by

loosened associations, neologisms and illogical constructs. Alterations may also be present in the way a person speaks, showing pressure of speech, speaking incessantly and quickly, derailment or flight of ideas, losing the train of thought, switching topic inappropriately, thought blocking and rhyming or punning.

The historical division of psychotic disorder into schizophrenia (non-affective) and manic-depressive (affective) illness derives from the extensive clinical work of Emil Kraepelin at the end of the nineteenth century. Kraepelin considered patients to be suffering from dementia praecox (later defined schizophrenia by Eugen Bleuler) and manic-depressive psychosis (bipolar disorder). The former applied when the patient was suffering from a long-term deteriorating condition; the latter when the patient was having distinct episodes of illness alternated with periods of normal functioning. Although modern classification divides the disorders assuming they reflect different aetiologies, different forms of psychosis have been described on a continuum of disorders, with schizophrenia at the most severe end of the spectrum (Crow 1986). Recently, both the dichotomous and the continuum views have been challenged by clinical and neurobiological studies, showing both overlaps and distinctions between affective and non-affective psychosis. A plausible model to explain overlaps and distinctions between schizophrenia and bipolar disorder should consider both common and unique risk factors. According to this model, certain susceptibility genes, shared by both disorders, may constitute a risk for psychosis in general, and the specific type of disorder developed may be the consequence of environmental exposure as well as genetic predisposition (Murray et al., 2004).

In schizophrenia and bipolar disorder confounders such as long-term illness or antipsychotic treatment may intervene and modify the basic pathological process clouding a clear understanding of these disorders. Studying individuals at the beginning of the illness process can limit the impact of these

confounders and help clarify the biological systems involved in the aetiopathogenesis of psychosis⁶. First episode psychosis defines the first time an individual experience psychotic symptoms. It identifies a clinically heterogeneous group encompassing both affective and non-affective psychoses. The incidence of first episode psychosis has been reported at 34.8 per 100,00 person per year in a study in the United Kingdom with higher incidence in south-east London compared to two other urban centres, Bristol and Nottingham (Kirkbride et al., 2006). Sixty-seven per cent of cases reported by Kirkbride et al. (2006) had a diagnosis of non-affective psychosis (37% DSM-IV schizophrenia and 30% DSM-IV other non-affective psychosis), 28% of the cases had a diagnosis of affective psychosis and the remaining 5% of case were diagnosed with a substance-induced psychosis. Risk factors for psychosis are urbanicity, migration, consumption of recreational drugs and exposure to trauma (Morgan et al., 2008). Studies in first episodes can limit the effect of confounders such as long-term illness, giving the opportunity to understand which neurobiological abnormalities are already present at the onset of the disorder. A further advantage of studying first episode psychosis is the short length of antipsychotic treatment, which may affect the biological systems involved in the aetiopathogenesis of psychosis. Moreover studies in first episode psychosis include different diagnoses across the spectrum, allowing a better understanding of which biological factors may differ between non-affective and affective psychosis.

⁶ Also in case of schizophrenia a diagnosis can be achieved only if continuous signs of the disturbance persist for at least 6 months (American Psychiatric Association, 2013a).

1.3 What is stress? What is trauma?

Environmental changes that require adaptation are often referred to as stress and stress is habitually regarded as a negative occurrence threatening the wellbeing of an individual (Sterling, 2012). This is mainly the consequence of the idea that stress challenges the homeostasis. The concept of a set point which characterises the normal level of functioning of each organ and apparatus and from which it deviates after stimulation, developed by Bernard and Cannon, has proven useful in understanding human physiology but hardly applies in real life (McEwen, 1993). Each activity of the body, such as endocrine production, glucose consumption and neural activity, is rarely characterised by steady activation but rather varies flexibly in response to environmental challenges and adjusts to the demands of the present stimulus as well as to each other organ's level of functioning. Adaptation to the environment, and therefore health, can be defined as a state of optimal dynamic variation in response to external demands (allostasis) instead of the conservation of a pre-set level of activity (homeostasis) (Sterling, 2014).

The physiological and behavioural reactions to physical or psychological stimuli result mainly from activations of the sympathetic nervous system and the Hypothalamic-Pituitary-Adrenal (HPA) axis, as well as from modulations in neurotransmitter and neuropeptide production and distribution (de Kloet, Joëls, & Holsboer, 2005). Effective allostasis results from a timely activation and termination of a stress response moulded on past experiences but plastic enough to change in response to the present circumstances (de Kloet et al., 2005). Each response to a stimulus is the consequence of the previous stimuli and prepares the ground for the new stimuli that follow (Herman, 2013). The characteristics of the stressors in terms of intensity, novelty, predictability, controllability as well as personal differences influence this process of adjusting to the environment (McEwen 1993). Each individual develops over time a repertoire of neurochemical, neuroendocrine and behavioural responses to the different

environmental challenges, which promotes a better or worse adaptation with various physical or psychological costs (McEwen 1993).

Interestingly, the effect of stress on the brain can be exemplified by an inverted U-shaped dose-response curve (Sandi and Haller 2015; Sapolsky 2015). Stressors exerting a mild to moderate amount of stress have proved to be beneficial for the brain architecture and function, whereas the complete absence of stress or a severely stressful and/or prolonged stimulation show detrimental effects of the same neurobiological endpoints such as reductions in spine and dendrite density, a decline in plasticity and finally an increasing of apoptosis (Robert M Sapolsky, 2015). As holding the “milieu intérieur” constant is not always the best solution, considering stress only a negative occurrence may not be the best approach either. Indeed environmental factors stimulate fluctuations in the stress response and this can determine two different outputs depending on their characteristics (McEwen, 1993; Sapolsky 2015). Mild to moderate stressors tends to kindle the adaptability of the individual, whereas stressors that overwhelm the person’s capability of coping tend to determine negative consequences over time (McEwen, 1993; Sapolsky 2015). Despite the fact that adaptation rarely comes without a cost ..., differences across individuals can be primarily considered the result of the varying ability to match the social and physical characteristics of the environment rather than the outcome of any dysfunctional process.(Del Giudice, Ellis, & Shirtcliff, 2011). My thesis focuses on the effect of severely stressful experiences, such as physical and sexual abuse in childhood, on brain structure and stress response in adults exposed and non-exposed.

1.3.1 Consequence of exposure to overwhelming stressful experiences in childhood

Although the lack of stimuli has unfavourable outcomes on development in itself, the exposure to stressors that overwhelm the individual's capability to adapt has more damaging results on physical and mental health (Heim et al., 2010). Traumatic events are associated with detrimental effects irrespective of the age of exposure. However, animal and human studies have shown that the most harmful and long-lasting consequences are associated with early exposure, which affects the functioning of endocrine, immune and central nervous systems (Heim et al., 2010). Since the seminal Adverse Childhood Experience study (ACE study) by Felitti et al (1998) a growing body of research has shown that exposure to adverse childhood experiences (i.e. emotional, physical, sexual abuse) has important and widespread effects on physical health (Putnam, Harris, & Putnam, 2010). This is even more concerning considering that in a study of a representative US sample of 17,337 participants, there was a prevalence of 10.6% for emotional abuse (women 13.1% and men 7.6%), 28.3% physical abuse (women 27.0% and men 29.9%), 20.7% sexual abuse (women 24.7% and men 16.0%), emotional neglect 14.8% (women 16.7% and men 12.4%), and physical neglect 9.9% (women 9.2% and 10.8%) (Felitti et al. 1998). These alarming estimates have been confirmed in a recent update of the same study in an increased sample, as well as in other studies (Felitti et al. 1998; Pérez-Fuentes et al. 2013). Individuals exposed to adverse childhood experience show poorer general health than people never exposed and higher odds ratios for the leading causes of death in adulthood, such as ischemic heart disease, cancer, chronic lung disease, skeletal fractures and liver disease (Felitti et al., 1998). Furthermore, the relationship between adversities and health outcomes appears to be graded, with higher odds ratios for those who had greater exposure to either the most severe or multiple types of abuse, indicating a cumulative effect of adversity on biological systems (Felitti et al. 1998; Gilbert et al. 2015).

Different mechanisms can help explain this widespread increase of adverse outcomes, as early-life adversity seems to contribute to potentially pathogenic pro-inflammatory phenotypes, alterations in the HPA axis, modulation of neurotransmission and changes in brain structure in adult individuals (Nemeroff and Binder 2014; Baumeister et al. 2015). Like the physical consequences, the psychological impact of

childhood adversity is so extensive that not being exposed to any type of childhood abuse is a protective factor against the risk of developing any kind of psychopathology later on in life (Putnam et al., 2010). Exposure to emotional, physical, and sexual abuse has consequences ranging from negative social outcomes, including impoverished social skills, higher criminality, and lower educational level, to the presence of negative emotions (comprising low self-esteem, anger, repressed hostility) and increased risk of developing a psychiatric disorder in adulthood (Varese et al. 2012; Carr et al. 2013). Subjects with severe psychiatric disorders are more likely to have experienced more frequent and more severe early adversities and psychological difficulties than people without past or current mental conditions (Mauritz et al., 2013). Varese et al. (2012) has shown that case-controlled, cross-sectional as well as prospective studies are consistent in reporting odds ratios between 2.75 and 2.99 of developing psychosis in adulthood in individuals who suffered physical, sexual, emotional abuse and physical or emotional neglect in childhood. Similarly, systematic reviews and meta-analyses show high odds ratios of developing personality disorder, especially borderline personality disorder, anxiety disorder, PTSD, depression and bipolar disorder in case of exposure to abuse or neglect (Lang et al. 2004; Carr et al. 2013; Varese et al. 2012; Mandelli et al. 2015). It has recently been shown that physical and sexual abuse are the most damaging type of experiences during childhood in terms of poorer physical health and more severe psychopathology and that their effect is still present when controlling for other types of abuse (e.g. neglect) (Green et al., 2010). A partial exception is emotional abuse in those who would later develop depression, which is shown to have a similar magnitude to either sexual or physical abuse by some studies (Mandelli, Petrelli, & Serretti, 2015). Furthermore, early-life adversity is associated with specific clinical characteristics of the patients, in depression, bipolar disorder and psychosis in a dose-response fashion (Lang et al. 2004; Heim et al. 2010; Putnam et al. 2010; Larsson et al. 2013; Berg et al. 2014). A more severe degree of abuse and a higher number of different types of abuse are associated with the presence of more severe symptoms and a more complex psychopathology in terms of coexisting internalizing and externalizing symptoms (Lang et al. 2004; Heim et al. 2010; Putnam et al. 2010; Larsson et al. 2013; Berg et al. 2014). In the case of depression, patients with abuse are more difficult to

treat and have an overall lower likelihood for remission (Heim et al., 2010). In psychosis, individuals with abuse are more likely to have more severe positive symptoms, hallucinations in particular (Uçok and Bikmaz 2007; Putnam et al. 2010; Berg et al. 2014).

Unfortunately several aspects of the effects of adverse experiences are still to be clarified (Heim et al. 2010; Putnam et al. 2010; Berg et al. 2014). The different types of childhood adversities (e.g. physical abuse, emotional neglect, parental loss) are inherently dissimilar in terms of characteristics (e.g. intentionality to harm) and severity, but they are often grouped together because of their relatively low prevalence (Heim et al., 2010). This practise limits our understanding of the mechanisms and the specific effect of each type of abuse (Heim et al., 2010). Furthermore, adverse experiences tend to cluster together, making it even more difficult to tease apart distinct impacts (Felitti et al. 1998; Suliman et al. 2009; Putnam et al. 2010). The ACE study was the first to show that there is a high co-occurrence of adverse childhood experiences, such that having suffered one increases the chance of experiencing two or more other adversities, with multiple-abused participants showing a more complex and more severe clinical picture especially if from a deprived background (Felitti et al. 1998; Suliman et al. 2009; Putnam et al. 2010).

This is particularly true for physical or sexual abuse; indeed, suffering these experiences increases the odds of having been exposed to any type of neglect as well (Suliman et al., 2009). As individuals with history physical or sexual abuse are more likely to have had more than one adverse experience than individuals with neglect, clustering together those individuals could imply mixing in the same group different pathological processes and levels of psychopathology. Moreover, the exposure to the first adverse childhood experience is thought to sensitise the individual to the impact of subsequent experiences in a non-linear fashion, further increasing the difference with individuals with just one traumatic experience in terms the biological mechanisms impacted by abuse (Heim et al., 2010). In light of this evidence, the common practise of using a linear score to determine the severity of adverse

experiences (with higher score indicating more severe level adversities) may lead to misrepresenting their impact. Finally, economic status seems also to play a different role in determining the outcome of child adversity depending on the type of experience (Green et al. 2010; Font and Maguire-Jack 2015). For example, in the case of neglect, parental socio-economical status explains a large amount of variance, while this is not the case for physical and sexual abuse, indicating that these latter types of abuse are more likely than other adversities to have a direct impact on the individuals' mental health (Font & Maguire-Jack, 2015).

Physical and sexual abuse emerge as the most psychologically damaging types of early adversities: these abuses explain the biggest amount of variance, in terms of both physical and mental health, and drive the overall effect despite occurring in individuals who have already been exposed to other, minor, types of abuse (Felitti et al. 1998; Suliman et al. 2009; Carpenter et al. 2009; Putnam et al. 2010). A sample encompassing only individuals with history of physical and sexual abuse in childhood is more likely to be homogenous than those including also other types of life adversities (e.g. neglect, loss) in terms of gravity representing individuals at the far end of the severity spectrum (Putnam et al., 2010). Furthermore, these specific types of abuse offer an opportunity to understand the mechanisms through which abuse exerts its influence, being less affected by differences in socio-economic status (Green et al. 2010; Font and Maguire-Jack 2015). Additionally, the study of individuals exposed to these adversities who do not later develop any form of psychopathology would greatly help in identifying the mechanisms that confer protection against these stressors.

1.4 Cortisol

1.4.1 The role of cortisol in the stress response

Demands of the environment vary over time, and the response to these demands needs to be flexible and appropriate. Every thriving human organism must be able to modulate the level of alertness, vigilance, arousal and metabolic consumption, as well as to master appropriate behavioural responses by either choosing from an established repertoire or creating a new one. In humans, the Hypothalamic-Pituitary-Adrenal (HPA) axis is pivotal in promoting adaptation and modulating recovery from the strains of the external environment. When a situation is perceived as stressful, either physically (e.g. running) or psychologically (e.g. talking with strangers), the brain activates many neuronal circuits to adapt to the new environmental demands, mainly through the activation of the HPA axis in an organised fashion (de Kloet et al., 2005). The initial reduction of the inhibitory (gabaergic) tone on the paraventricular nucleus in the hypothalamus facilitates the release of the Corticotropin-Releasing-Factor (CRF), which stimulates in turn the release of the Adrenocorticotropic Hormone (ACTH) from the anterior pituitary gland. Once the ACTH is secreted in the blood stream, it is able to reach the adrenal glands, situated bilaterally on the apical parts of the kidneys, to stimulate the production and the release of the main stress hormone in humans, cortisol (de Kloet et al. 2005; Stephens and Wand 2012) (figure 1.1).

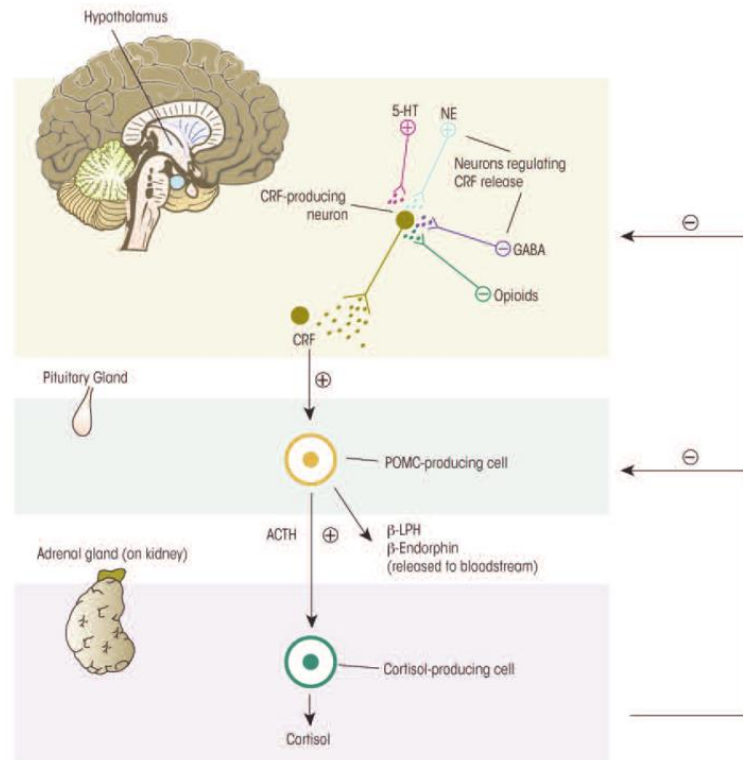


Figure 1.1: The production of Corticotropin-Releasing-Factor (CRF) from the paraventricular nucleus in the hypothalamus stimulates the release of the Adrenocorticotrophic Hormone (ACTH) from the anterior pituitary gland. ACTH in turn stimulates cells of the adrenal glands to produce and release cortisol (Adapted from Stephens and Wand 2012).

Depending on how stressful a situation is, the levels of cortisol increases or decreases in the blood stream, reaching every organ and allowing the coordination of brain and body functions. Cortisol is produced by the adrenal gland in secretory burst of around 20 minutes in response to stimuli and in a circadian rhythm with increased concentration in the morning and reduced in the evening (Young, Abelson, & Lightman, 2004). The main roles of the HPA are to mobilise metabolic and behavioural responses to sustain the basal activity of the organism and respond to intervening stressors. This is also reflected in the type of receptors the cortisol hormone binds to. Mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) bind cortisol with a tenfold difference in affinity, hence the GR responds to bursts of hormone secretions while the MR to the circadian production to coordinate the acute and late-recovery phase of the adaptive stress reaction respectively (de Kloet et al., 2005). The HPA axis can be activated in a wide range of circumstances: either by reduction of the cortisol level, monitored by GR in the paraventricular

nucleus, or through limbic pathways in response to psychological stressors or through brain-stem pathways in the case of visceral and sensory stimuli (Sapolsky, et al., 2000). Cortisol modulates the release of neurotransmitters and the electrical activity of neuronal networks, and influences gene expression. Cortisol also mobilises substrates for energy metabolism, dampens the immune and inflammatory reactions and along with catecholamines promotes a fight-flight response in the short term (de Kloet et al. 2005; Stephens and Wand 2012). In the long term, cortisol reduces metabolic consumption and stimulates consolidation of memories and future retrieval (de Kloet et al., 2005). The dualism of actions in promoting and moderating higher order processes carried by cortisol is epitomised exceptionally well by the distribution of MR and GR in the brain (de Kloet et al. 2005; Stephens and Wand 2012). Co-expression is indeed reported in cortical areas, dentate gyrus, lateral septi and hippocampal pyramidal cell fields with the partial exception of the CA3 (Patel et al., 2001). The maintenance of dendritic structure and size in the dentate gyrus depends on the effect of MR occupancy on proliferation and apoptosis while the neurogenesis is regulated by the balance between MR and GR stimulation (Herbert et al., 2006). Corticosteroid through GR can impact the electrical activities of neurons and regulate the calcium influx - thus the release of neurotransmitters, but only when the cells are already activated. This confirms that enhanced cortisol levels would facilitate responses according to existing predispositions (Goette, Bendahan, Thoresen, Hollis, & Sandi, 2014). The HPA axis is involved directly and indirectly in memory processes. Corticosteroid, acting on GR and MR alike, can facilitate memory formation inducing long-term-potentialiation (LTP) in the hippocampus. However, excessively high levels have been reported to impair LTP and cause long-term depression, while storage of information for future use depends on GR activation (de Kloet et al., 2005; Herbert et al., 2006). Arousal is known to increase the persistence of memory. Promoting activation, the HPA axis indirectly impinges on memory consolidation through moderation of a neural network that encompasses the amygdala, the hippocampus and the prefrontal cortex (de Kloet et al., 2005; Herbert et al., 2006). These multiple effects of cortisol are finely dependant on the hormone concentration in an inverted U-shaped fashion (de Kloet et al., 2005). The widespread damaging impact of excessive cortisol exposure has been long studied since

the seminal study by Sapolsky in 1985. Too high a cortisol concentration impacts brain structure detrimentally, altering the dendritic morphology, the length of the neural network and the mobilisation of neurotransmitters triggering corticosteroid toxicity in tissues rich in MR and GR such as the hippocampus (Teicher et al. 2012 ; de Kloet et al. 2005). In the last decade, somewhat surprisingly, it has emerged that similar consequences in these tissues can also result from too low a cortisol production, as both ends of the cortisol concentration curve produce strikingly similar outcomes (Teicher et al. 2012 ; de Kloet et al. 2005).

1.4.2 Abnormal cortisol concentration in individuals exposed to childhood maltreatment

The extent of behavioural control that can be exerted over a stressor reduces its potentially damaging impact. A stressor perceived as controllable (e.g. knowing how long one should run, or being exposed to the same stressor over time) seems to limit the HPA axis activation consequent to stress exposure. It does not therefore come as a surprise that experiencing abuse and maltreatment, where controllability is minimal if not absent, can considerably challenge the capacity of the stress response system and have far reaching impact on the organism as a whole (de Kloet et al., 2005). It has been thought that failure of coping after stressful experiences in childhood may alter the regulatory mechanisms of cortisol secretion, which can result in a long-lasting state of distress, that is reflected in aberrant HPA axis activity, altered limbic function and abnormal behaviour (Sandi & Haller, 2015). For example, studies in both rats and mice show that treatment with high doses of corticosteroid in the young animal reduce adult social explorations and elicit submissive behaviours, as does exposure to perinatal stress (Sandi & Haller, 2015). In humans, early exposure to abuse affects HPA axis activity and enhances the neuroendocrine reaction to emotional stimuli. It has been proposed that this may pave the way for the abnormal cortisol concentrations and brain abnormalities found in adulthood in these individuals (Sandi & Haller, 2015).

Studies consistently show increased plasma levels of diurnal cortisol in children and pupils of prepuberal age with and without psychopathology, which are often accompanied with high levels of Corticotropin-Releasing-Hormone (CRH), responsible for increasing the production of cortisol, and pituitary hypertrophy, the gland to which the CRH binds (M. De Bellis, Spratt, & Hooper, 2011). Exposure to life adversities in childhood is associated with abnormal glucocorticoid secretion in adulthood as well with a reduction in the size of the hippocampus (Martin H. Teicher et al., 2003). Interestingly, this abnormality is not reported in children with a history of exposure to trauma, suggesting that the full impact of abuse probably emerges at a later stage, perhaps from an interaction between traumatic experiences, other risk factors and the trajectory of brain maturation (Martin H. Teicher et al., 2003).

Although increased levels of diurnal cortisol have been reported quite consistently in individuals exposed to early abuse, the effects of childhood adversity on cortisol reactivity to stress have been less consistent (Lupien et al. 2009; De Bellis et al. 2011). In particular, some studies in adults who experienced childhood adversity report reductions in the capacity of the HPA axis to respond to a stressor, while others report an increase in cortisol secretion (Carpenter et al. 2009; Heim et al. 2010). These differences may be explained by various factors: 1) the impact of gender, as women with a history of abuse in childhood show an increased reactivity to stress, whereas men show a decreased reactivity, 2) the methods through which exposure to adverse life experience are assessed and classified (Heim et al. 2010; De Bellis 2001; Doom et al. 2013), and 3) the different proportion of healthy individuals and subjects with psychopathology included across different studies (Strüder, Strüder, & Roth, 2014).

1.4.3 Abnormal cortisol level in psychosis

Increased cortisol levels have been consistently found in the active phases of schizophrenia or psychosis in chronic patients as well as in a first episode (Mondelli et al. 2010; Borges et al. 2013; Karanikas et al. 2014). Glucocorticoids have been shown to increase brain dopaminergic release and since excessive dopamine concentration in the mid-brain is one of the most replicated results in psychosis and schizophrenia, this may help to explain how the cortisol deregulation present in these disorders may be linked the development of psychosis (Walker & Diforio, 1997). Indeed, in individuals at risk of developing psychosis, the activation of the stress system, when coupled with increased striatal dopamine synthesis, seems to be specific to those individuals who then develop a psychiatric disorder (Walker et al, 1997; Howes et al. 2011). Glucocorticoid hormone concentration, either too high or too low, ceases to protect neurons and rather produces a detrimental effect in areas rich in glucocorticoid receptors (i.e. hippocampus, frontal cortex and amygdala) (Mcewen et al. 2015). Depending on the concentrations, effects include stark retraction of dendrites, reduction of the synapse density, impairment of cellular turnover and the induction of neuronal apoptosis (Mcewen et al. 2015). As cortisol increases the release of glutamate, its affect can arise independently of the binding of glucocorticoid receptors in time and space leading to the stress-induced remodelling of dendrites and synapses as well as excitatory toxicity in the hippocampus and in the frontal and prefrontal cortices with permanent changes in activation and length of neuronal circuitry (Arnsten 2015; Mcewen et al. 2015). Interestingly, compared to healthy controls, patients at first episode of psychosis show altered glucocorticoids secretion, with increased cortisol production during the day and a blunted cortisol awakening response, where healthy controls show an increase within the first hour after awakening, and a reduced response to social stressors (Mondelli et al. 2010; Pruessner et al. 2013). Also, in individuals at risk to develop psychosis, an altered HPA axis activity profile is present, with a reduction in reactivity, as shown by a blunted cortisol response to psychosocial stress, although this has not always been shown consistently (Pruessner et al. 2013; Labad et al. 2015). Furthermore, in a recent meta-analysis I have shown how the cortisol levels increase in response to a psychosocial stress in depression to a level similar to that of healthy controls,

whereas in schizophrenia patients there is a blunted cortisol response compared with controls. This response differentiates these disorders, which are otherwise both characterized by increased basal cortisol levels (Ciufolini, Dazzan, Kempton, Pariante, & Mondelli, 2014). Glucocorticoid levels have also been proven to be a useful indicator of the clinical course of psychosis, as a smaller cortisol increase at awakening, as well as higher inflammatory cytokines levels, have been found to predict a poor response to 12-week treatment (V. Mondelli et al., 2015).

An indirect measure of HPA activity is also the size of the pituitary gland that may change in volume when exposed to conditions of chronic stress (Dedovic et al. 2009; Herman 2013). The volume of the gland has been found to be significantly larger in patients at the time of the first psychotic episode, indicating again an anomalous activation of the axis (Pariante et al., 2005). The pituitary gland has also been found larger in subjects who later developed psychosis compared to those at risk but who did not develop any psychosis (Garner et al., 2005). Furthermore, the gland was larger the closer these individuals were to developing the illness, suggesting an activation of the axis coincided with the onset of the symptoms (Garner et al., 2005). The activation of the stress response is relevant as there is evidence that a variety of brain structures are affected, for example, by high cortisol levels. In line with this evidence, work from my supervisors has found that in patients with first episode psychosis, the disrupted HPA axis activity appears to be associated with smaller hippocampal volumes (Mondelli et al. 2011). Furthermore, gender differences in the hippocampus are emerging in patients at first episode psychosis, with men showing a reduction in volume, a reduction also related with a blunted cortisol production at awakening in the left side, when compared with women (M. Pruessner et al., 2015). This anatomical differences may also help to explain different patterns of cortisol reactivity based on gender in individuals at the onset of psychosis (M. Pruessner et al., 2008). It is therefore plausible that some of the brain alterations often seen in psychosis may be related to an abnormal reactivity of the stress response system reported in this disorder, as an altered concentration of corticosteroid from adolescence to adulthood can

damage the hippocampus and this in turn may have a negative impact on the HPA axis regulation leading a feed-forward loop that increases the hormone secretion (Karanikas et al., 2014).

Some of the consequences of exposure to abuse seem to partially overlap with the biological abnormalities present in psychosis. For example, childhood trauma has been found to be associated with higher cortisol levels and smaller hippocampal volume and these abnormalities have been also found at the onset of psychosis (Dedovic et al. 2009; Mondelli et al., 2010). However, the full impact of trauma has not yet been clarified. Determining cortisol production in individuals at their first episode of psychosis, when the functional changes associated with chronicity have not yet occurred, and in healthy controls exposed and not exposed to childhood trauma, will help elucidate the role of stress response in the development of the illness.

1.5 Brain structure

1.5.1 Brain abnormalities in individuals exposed to childhood maltreatment

Brain maturation is a complex topographically distributed process that spans across decades, involving coordinated changes over time in structures (e.g. thinning of the cortex, increasing white matter volume), along with fine-tuning of the network (e.g. changes in connectivity, optimisation of the connections). Thus it is not surprising that exposure to stressors that can overwhelm the capability of an individual to cope can negatively influence this finely regulated process, with widespread impact on cellular metabolism, release of neurotransmitters and developmental trajectories (M. De Bellis et al., 2011).

Animal models show that increased levels of stress decrease neuronal branching and induce apoptosis in the prefrontal cortex, hippocampus and hypothalamus with a corresponding reduction in grey matter volume, mainly through the rise in corticosteroid concentrations and an overactivation of the noradrenergic system (Sandi & Haller, 2015). The same rat and mouse models show that attempts to cope with those stressors can lead to over-activation in areas of the brain that regulate emotions (i.e. amygdala, prefrontal cortex) or neurotransmitter systems (i.e. serotonin, dopamine), inducing abnormal behaviours (i.e. pathological aggression) (Sandi & Haller, 2015). Interestingly, the first gene-environment interaction study in humans found that the polymorphism of an enzyme involved in the metabolism of dopamine (MAO-A) modulates the likelihood that children exposed to early maltreatment would develop an antisocial behaviour (Caspi et al., 2002). In addition, the over-activation of the amygdala in response to negative emotions is a well replicated finding in individuals with a history of abuse (Dannlowski et al., 2012). Furthermore, human studies confirm a widespread effect of trauma in brain regions at the interface between the incoming sensory information and the appraisal process, such as the

limbic brain structures hippocampus and amygdala as well as the prefrontal cortex (de Kloet et al., 2005). Children exposed to maltreatment show reduced grey matter volume in the medial orbitofrontal cortex, and a reduction in cortical thickness in an extended cluster that incorporates the anterior cingulate, superior frontal gyrus, and orbitofrontal cortex, accompanied by reduced local gyrification within the lingual gyrus and the insula (Kelly et al. 2013; De Brito et al. 2013). These alterations appear to become more spatially distributed with age (Edmiston et al. 2011; Dannlowski et al. 2012; Lim et al. 2014). Indeed adolescents with childhood abuse exposure have a reduction in grey matter volume in the left middle temporal gyrus and prefrontal cortex, striatum and amygdala, while adults with a history of abuse in childhood show reduction in grey matter volume in superior temporal, inferior orbitofrontal, middle temporal, parahippocampal gyrus, the insula, amygdala and hippocampus on the right hemisphere and inferior frontal, postcentral and precentral gyrus on the left hemisphere (Edmiston et al. 2011; Dannlowski et al. 2012; Lim et al. 2014). Furthermore, adults with a history of trauma show an increase in grey matter volume in the right superior frontal and medial superior frontal gyrus and in the left middle occipital, superior occipital, inferior parietal and angular gyrus in adulthood (Lim et al., 2014). This may be result from a delay in the developmental trajectories due to the occurrence of abuse (Tomoda et al., 2009). The way different parts of the brain are interconnected to each other has been successfully approximated to a network whose nodes are discrete brain regions (Bullmore, Bullmore, Sporns, & Sporns, 2009). The nodes with the highest number of communications, therefore central in the structure of the system, are known as hubs (Bullmore et al., 2009). Experience of abuse is associated with a different profile of interconnection between the different parts of the brain. For example, the left anterior cingulate, a hub in healthy people, shows reduced connectivity in the network of intra-hemisphere connections in individuals exposed to abuse. Conversely, areas such as the right anterior insula and precuneus, which are not hubs in healthy individuals, become hubs in people with history of abuse in childhood (Martin H. Teicher, Anderson, Ohashi, & Polcari, 2014).

Similarly to the partial overlap between the consequences of abuse on the HPA axis and the cortisol alterations present in psychosis, it is interesting to note that the abnormalities found in healthy individuals exposed to childhood abuse (the reductions in grey matter volume in the hippocampus, in the corticostriatal-limbic area and reduced activity of the ventral striatum) correspond to key regions of the brain affected in psychosis (Edmiston et al 2001; Nikolova et al., 2012; Teicher et al., 2012). Furthermore, a recent study found an association between HPA axis hyperactivity and reduced grey matter volume in the right middle cingulate in individuals exposed to childhood trauma (Lu et al., 2013). There have been only a few studies, on small samples, exploring the association between childhood exposure to trauma and brain structure in patients with schizophrenia, but those conducted to date are consistent in showing an association between trauma exposure and reduced grey matter volume in the prefrontal cortex, and smaller hippocampal and amygdala volumes (Aas et al., 2012; Hoy et al., 2012; Sheffield et al. 2013). At first episode psychosis the Brain Derived Neurotrophic Factor (BDNF) is lower compared with healthy controls (Valeria Mondelli et al., 2011). Additionally the presence of a polymorphism that reduces the production of the Brain Derived Neurotrophic Factor (BDNF), a neurotrophic factor important in brain development and plasticity, is associated with a reduction in right hippocampal volume, larger ventricles bilaterally, and cognitive deficits (Aas et al., 2013). Finally, work from my supervisors has shown that in patients with first episode psychosis, reduced levels of BDNF are associated with smaller left hippocampal volume (Valeria Mondelli et al., 2011). The partial overlap between alterations in brain regions and biological pathways, in psychosis and in individuals with history of childhood abuse, may hint that the exposure to abuse at an early age increases the risk of psychosis impacting functions already vulnerable in those individuals.

1.5.2 Brain abnormalities in psychosis

It is well established that schizophrenia is a disease characterised by neuroanatomical abnormalities spatially distributed in the brain (Wright et al., 2000). Patients with chronic schizophrenia show a global reduction of cerebral volume and ventricular enlargement. Also, a decrease in grey matter is often present in the frontal and medial temporal lobes (amygdala, hippocampus and parahippocampal gyrus), the thalamus, and superior temporal gyrus. In addition, subcortical structures like the globus pallidus and caudate seem to be reduced in volume in antipsychotic-naïve individuals but increased after antipsychotic drugs are started (Wright et al., 2000; Mamah et al., 2007). A meta-analysis of longitudinal studies showed that schizophrenia is characterised by a reduction of grey matter in the frontal and superior temporal structures especially in the left hemisphere and in the first stages of the disease, despite a partial moderation by the type of pharmacological treatment (Vita, De Peri, Deste, & Sacchetti, 2012). These neuroanatomical changes may, at least to some extent, be the result of confounding factors such as medication, and this has been confirmed by a meta-analysis which found an association between medications and the reduction of grey matter in individuals with schizophrenia in the same regions known to be altered in the disorder (Torres, Portela-Oliveira, Borgwardt, & Busatto, 2013).

Evaluating patients with First Episode Psychosis (FEP) or individuals at High-risk (HR) of developing psychosis, in which most of the previous confounding factors are reduced if not virtually absent, allows researchers to make inferences regarding how the brain changes early on in the disorder. Studies on these populations show that structural abnormalities are already present at the beginning and in the prodromal phase of the psychotic illness (Morgan et al., 2007; Dazzan et al. 2012). The increase of Cerebrospinal Fluid (CSF) is among the most consistent and replicated results (Steen et al., 2006; Vita et al., 2006). As chronic patients, those at first episode also show reductions in grey matter in frontal and temporal cortices (Steen et al., 2006; Ellison-Wright et al. 2008; Nenadic et al., 2013). Structural abnormalities have been also reported in pre-frontal, medial and inferior temporal gyrus (de Castro-Mangiano et al., 2012). Most of these findings have been identified in studies that evaluated a priori selected regions of interest (ROI).

Although this approach is useful, there may be a bias in the regions selected for analysis. For example, the fact that ROIs are spatially restricted and usually limited to parts of the brain that are easy to measure may result in over-representation of some areas. Also, it may produce less reliable measures for complex brain areas (Wright et al., 2000). Nonetheless, these findings have been confirmed by the implementation of voxel-based methods, a technique that can examine both changes in specific areas and in the brain as a whole (Wolin et al., 1998; Wright et al., 1999). Furthermore, grey matter reductions have been shown in left superior and medial temporal gyrus, post-central gyrus and right temporal inferior gyrus (de Castro-Mangiano et al., 2012). Reductions in grey matter have also been observed in the thalamus and caudate, as well as in the amygdala and hippocampus (Steen et al., 2006; Ellison-Wright et al., 2008; Aas et al., 2011; Walter et al., 2012).

Some of these abnormalities are also associated with later transition to psychosis in HR studies. Indeed, high-risk subjects who subsequently make a transition to psychosis show relatively reduced regional grey matter in the insula, anterior cingulate, prefrontal cortex and cerebellum (Pantelis et al., 2003; Nakamura et al., 2013). In addition, an enlargement of the pituitary gland seems to be associated with an increased risk of psychosis (Garner et al., 2005). A recent meta-analysis adds evidence to the previous findings by highlighting structural abnormalities in medial temporal, prefrontal, anterior cingulate and insular cortex that might be most predictive of the development of psychosis, which seem to occur at slightly different stages of the process (P. Fusar-Poli, Smieskova, Serafini, Politi, & Borgwardt, 2012). While subtle reductions in cingulate, insular and prefrontal regions appear to be present already in the prodromal stage, some of the cortical gray matter abnormalities observed in patients with the established illness seem to occur during the acute phase of transition to psychosis, and other brain structural changes, like volume reductions in the superior temporal gyrus, may emerge as psychosis develops (Smieskova et al., 2010).

Even though neuroanatomical changes at the time of the onset of psychosis are subtle and spatially distributed, they are consistent and partially overlapping with the findings from patients with chronic

schizophrenia. In fact, more marked and distributed brain changes seem to occur with illness progression (Vita et al., 2012)

Psychosis thus appears to be a dynamic process, characterized by the presence of neuroanatomical abnormalities that precedes the clinical onset (during the putative prodromal phase), which become increasingly marked and distributed later on. It is therefore possible that an abnormal response to environmental challenges or exposure to stressors at a vulnerable age (such as abuse during childhood) plays a role in increasing the risk for the onset of psychotic symptoms, with consequences on brain structure.

1.6 Rationale for the study

Experiencing physical or sexual abuse during childhood is a major stressor and a risk factor for psychosis; however, the reason why some individuals who are exposed to this abuse develop psychosis while others exposed to the same abuse do not is still unclear (Robert M Sapolsky, 2015). Evidence from the general population shows that exposure to childhood abuse affects the functioning of the endocrine and central nervous systems with long-lasting consequences (Nemeroff 2004; Lupien et al. 2009). In particular, these experiences have been linked with alterations the HPA axis and its reactivity, and abnormalities of brain structure resulting in aberrant neuroendocrine and behavioural responses (Teicher et al. 2006; Heim et al. 2010). Furthermore, physical or sexual abuse has the most severe consequences in term of physical and mental health with its effects minimally influenced by the co-occurrence of other minor types of abuse and by the co-occurrence of other socio-economic factors (Putnam et al., 2010). Nonetheless, the impact of trauma on HPA axis activity and brain structure mimics and sometimes overlaps with the biological abnormalities present in individuals with psychotic disorders, the pathway that leads from childhood abuse to the onset of psychosis has still not been defined.

1.6.1 This thesis

The aim of this project is to delineate the biological mechanisms through which physical and sexual abuse increase the risk of psychosis. The objectives are to investigate the presence of a pattern of abnormalities in brain structure and in the activity of the Hypothalamic Pituitary Adrenal HPA axis in people at their first episode of psychosis and healthy controls, with and without a personal history of childhood abuse. In particular, I use structural MRI (sMRI) to evaluate structural differences in the brain and salivary cortisol levels at multiple time-points during the day as measures of HPA axis activity, between those who were exposed to childhood abuse and those who were not. Neuroimaging and biological findings are then integrated to define a biological process that may contribute to the onset of psychosis in subjects who suffered childhood physical or sexual abuse. Having a sample that includes healthy individuals with and without history of physical and sexual abuse provides an unparalleled opportunity to understand the mechanisms through which abuse may exert its influence; indeed, studying people exposed to severe childhood adversities but who do not develop any form of psychopathology can greatly help to identify the mechanisms conferring resilience against those stressors.

1.6.2 Primary research questions

Are there differences in brain structure (as measured with sMRI) and HPA axis activity profile (as measured by salivary cortisol) between individuals exposed and non-exposed to childhood abuse?

- If so, are there differences in brain structure and HPA axis activity profile between patients at first episode psychosis and healthy individuals exposed to childhood abuse?

- Are there differences in brain structure and HPA axis activity profile between patients exposed and not-exposed to childhood abuse? And similarly are there differences in brain structure and HPA axis activity between healthy individuals exposed and not-exposed to childhood abuse?

- Are the effects of abuse on HPA axis activity and brain structure influenced by gender (i.e. do male and female participants show distinctive abnormalities in the HPA axis activity and brain structure)?

- Is it possible to integrate neuroimaging and cortisol data to define the biological pathways promote the association between childhood trauma and onset of psychosis?

1.6.3 Hypotheses

Individuals exposed to childhood abuse, irrespective of being either patients or healthy controls, will show smaller frontal regions (prefrontal cortex, anterior cingulate). They will also show reduced

reactivity of HPA axis activation in response to physiological stress (as measured by the cortisol awakening response) and increased basal cortisol production (as measured by the level of cortisol during the day).

1. Patients and healthy individuals exposed to childhood abuse will show similar abnormalities in the frontal regions (pre-frontal cortex and anterior cingulate) and in the HPA axis activity (cortisol awakening response and level of cortisol during the day) but to a lesser extent in healthy individuals (i.e., they will be intermediate between those of non-exposed patients and non-exposed healthy controls).
2. Patients exposed to childhood abuse in comparison with non-exposed patients will show smaller frontal (prefrontal cortex, anterior cingulate) and medial temporal regions (amygdala and hippocampus). Healthy individuals exposed to childhood abuse in comparison with non exposed will show similar abnormalities to patients exposed to abuse but to a lesser extent.
3. Female and male individuals will present different patterns of brain structural abnormalities (i.e. abnormalities would be present in different brain areas) and HPA axis activity (i.e. female participants would present more blunted reactivity than male participants).
4. There will be a negative correlation between the volume pre-frontal areas associated with structural alterations in individuals (both cases and controls) with a history of childhood abuse and the Cortisol Awakening Response with respect to ground (CARg) and the basal cortisol levels.

2 Methods

“The move is there, but you must see it.”

Savelij Grigor'evič Tartakover⁷

⁷ Polish and French chess grandmaster.

Overview of the methods

In this project I want to delineate the possible relationships between physical and sexual abuse and brain structure, as well as HPA axis activity, in individuals with and without psychosis. The analysis has been planned and conducted at two levels. Firstly, the effects of abuse on brain structure and the effect of abuse on HPA axis activity have been investigated separately. Secondly, a further analysis has examined both brain structure and HPA axis activity to explore whether alterations in these two biological systems are related to each other.

Section 2.1 of this chapter describes the research design, the recruitment process, the socio-demographic and clinical data of the sample included and the statistical analyses conducted to analyse them. Section 2.2 outlines the acquisition of the data and the analyses conducted to study the presence of abnormalities in brain structure in relation to childhood abuse (Structural MRI methodology); Section 2.3 describes the HPA axis activity abnormalities associated with the exposure to childhood abuse (Hypothalamic-pituitary-adrenal (HPA) axis function methodology); and finally, Section 2.4 describes the methodology used to examine the potential relationship between the two biological systems (association between structural MRI measures and Hypothalamic-pituitary-adrenal (HPA) axis function) in individuals with history of abuse in childhood.

2.1 Research design

The sample I include in my study is part of two larger observational case-control studies: the cross-sectional Wellcome Trust study on Childhood Trauma and Psychosis, and the longitudinal BRC Psychosis Theme study on Genetics and Psychosis. The recruitment for the BRC Psychosis Theme study on Genetics and Psychosis study started in March 2008 and finished in April 2011. The recruitment for the Wellcome Trust study on Childhood Trauma and Psychosis started in April 2011 and finished in August 2014. Assessments conducted as part of these studies are identical and include the collection of socio-demographic data, clinical data and neuroimaging evaluation of brain structure with MRI. Both studies also include the evaluation of traumatic experiences during childhood using the Childhood Experience of Care and Abuse Questionnaire (CECA-Q) (Bifulco, Bernazzani, Moran, & Jacobs, 2005). Shortly after having consented to the studies, participants were asked to collect saliva samples (for the evaluation of the biological response to stress) at six defined time-points, from awakening to 8 pm. From this point onward I will therefore refer to the samples as a single dataset.

2.1.1 Recruitment procedure

A sample of first episode psychosis patients (FEP) was recruited from the South London and Maudsley (SLAM) catchment area from both inpatient and outpatient services. The SLAM catchment area includes the Maudsley, Lambeth and Bethlem Royal Hospitals, which provide care to a large area of South London, encompassing the boroughs of Lambeth, Southwark, Croydon and Lewisham (figure 2.1).

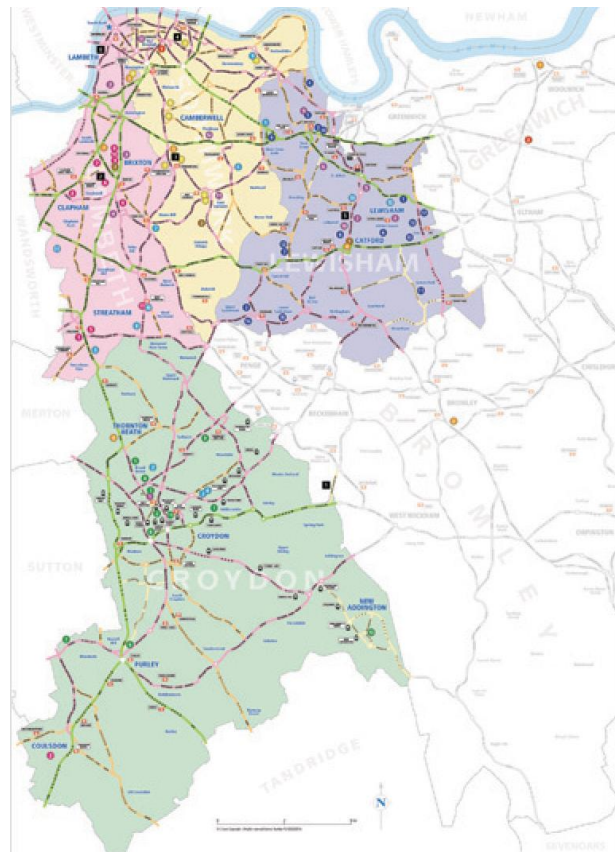


Figure 2.1: South London and Maudsley (SLAM) catchment area

2.1.2 First episode psychosis patient sample recruitment

Individuals presenting to psychiatric services for the first time with psychotic symptoms of at least one-week duration were recruited for the study. The recruitment strategy was based on contacting inpatients and outpatients services regularly, interviewing staff and reviewing clinical notes, and approaching all subjects aged 18 - 65 who presented for the first time to these services for a functional psychotic illness and who met the following criteria:

- Age 18 - 65 years;
- Resident within the study area;
- Absence of a moderate or severe learning disability as defined by ICD-10 (World Health Organisation, 1992);
- Presence of a functional psychotic illness (ICD-10 F10-19, excluding coding F1x.0 for acute intoxication; F20-29 and F30-39, psychotic codings) (World Health Organisation, 1992);
- No previous contact with psychiatric services for symptoms of psychosis.

Potential participants were excluded if they met any of the following exclusion criteria:

- Not a fluent English speaker (i.e. requires a translator).
- Presence of psychosis due to an organic cause.
- Previous head trauma and/or loss of consciousness for more than 1 hour.

The local Ethical Committee approved the study (05/Q0706/158). After individuals received the complete description of the research, written informed consent was obtained.

Potential participants who met inclusion criteria were consented to the study as soon as possible after their first presentation to services and within 3 months from first presentation. On meeting the inclusion criteria, an agreement to undergo an MRI scan was obtained; consequently, an MRI safety-screening questionnaire was administered. The questionnaire included questions regarding circumstances that could prevent the individual from safely undertaking the MRI scan (e.g. metal within the body, recent surgery, claustrophobia). If any questions were answered 'yes' then the participant did not undergo the procedure.

2.1.3 Healthy control sample recruitment

A sample of healthy controls was recruited from the same catchment area served by the South London and Maudsley (SLAM) to be as similar as to the patient group in terms of age, gender, ethnicity, educational qualifications and employment status,. The recruitment was conducted using different methodologies, which included advertisement in local newspapers, community centres and job centres, leafleting in the local area and through three volunteer databases - Mindsearch (www.mindsearch.com), BRC controls database and Biotrax (www.biotrax.com). In the recruitment of control populations there is always a potential for bias, for example when recruiting controls mainly from student population or hospital staff. The various approaches used by this study has minimised selection bias. Individuals interested in participating were contacted by telephone and screened using the Psychosis Screening Questionnaire (Bebbington & Nayani, 1995). They were excluded if they reported any psychotic symptom or had history of any psychotic illness, or fulfilled the criteria for any Axis I clinical disorder at the moment of recruitment. If the participants were considered suitable, they were invited to the Institute of Psychiatry, Psychology and Neuroscience, where written informed consent was obtained.

2.1.4 Socio-demographic and clinical characterisation of the sample

During the study assessments a large number of socio-demographic and clinical information were obtained from all participants. This project included some of these socio-demographic variables and the evaluation of the abuse exposure for the entire sample as well as information about the clinical features of patients at their first episode of psychosis.

2.1.4.1 Socio-demographic variables

The socio-demographic variables were chosen in order to describe the composition of the sample and quantify the level of social functioning of participants. These variables include age, gender, ethnicity (self-ascribed by the participants), occupational status and living circumstances.

2.1.4.2 Evaluation of the abuse exposure

Although prospective measures of childhood maltreatment are frequently considered ideal, it is very difficult to collect such sensitive material at the time of abuse, especially if the perpetrator is a member of the family; parents information are unlikely to reliably provide accounts and it is clear that ethical and practical problems also associated with the interviewing of children. Furthermore investigating in a prospective study the impact of childhood abuse on a relatively low prevalence condition, as psychosis, would have required the recruitment of thousands of individuals and the execution of thousands of interviews over a period of time of decades to identify the same number of individuals affected by the illness. The economical and logistical cost of such study would have been disproportionally high. The Childhood Experience of Care and Abuse interview, as well as its later derived shortened version the Childhood Experience of Care and Abuse Questionnaire (CECA-Q), was specifically designed to reliably elicit retrospective reports of childhood adversity, using an investigator-based - as opposed to respondent-based - measurement (Bifulco et al. 1994; Bifulco et al. 2005). This intensive semi-structured interview provides detailed information about childhood adversity before the age of 17 (i.e. household discord, and psychological, physical, and sexual abuse), as well as information on family living arrangements, and parental separation and loss, amongst other adversities. The CECA-Q was developed from the CECA

interview mirroring its distinctive features with a less broad focus, it explores the occurrences of adverse experiences during childhood in terms of parental care (neglect and antipathy from parents), physical and sexual abuse; the items on physical and sexual abuse are virtually identical to those of the CECA (Bifulco et al., 2005). Because of a change in protocol, 57% of the participants were assessed using the CECA-Q and 43% with the CECA. Both the CECA and the CECA-Q were administered as semi-structured interviews. Different characteristics of the scale serve the purpose of ensuring interviews are well standardised, accurate and reliable, and ensure an accurate coding of the experiences (Bifulco et al. 1994; Bifulco et al. 2005). In order to reduce the likelihood of respondent bias, which is often associated with self-report measures of childhood adversity, the interview provides manualised examples, and strict coding guidelines, where the investigator, rather than the respondent, decides whether the experience meets the predefined thresholds for occurrence and severity. The interview focuses on behaviours and practical details of the participants' experiences, as opposed to the emotional reaction to the stressors, in order to capture the objective, rather than the subjective, details of the event, thus reducing reporting bias. Furthermore, respondents are encouraged to relate their answers as stories to improve memory recall and to enable the researcher to obtain a full and coherent picture of the experience. Finally, unlike many other measures of childhood adversity (such as the Child Abuse and Trauma Scale (Sanders and Becker-Lausen 1995), the CECA and the CECA-Q collect a wealth of information on the severity, frequency, duration of the abuse, as well as the degree of severity and the chronological order of the adversity. Moreover, the interview has proven to be a reliable way to collect information on abusive experiences in childhood. For example, Stein et al. (2004) found a high level of agreement between data collected using the CECA interview and community records within a sample of 77 individuals ($\chi^2 = 5.75$, $p < 0.01$). Similarly, Fisher et al. (2011) found that the CECA-Q had good levels of convergent validity with clinical case notes in a sample of patients with psychosis (sexual abuse: $\kappa = 0.526$, $p < 0.001$; physical abuse: $\kappa = 0.394$, $p < 0.001$), and showing that patients' reports were stable over a 7-year period (sexual abuse: $\kappa = 0.590$, $p < 0.01$; physical abuse: $\kappa = 0.634$, $p < 0.001$). During the assessment in our study further measures were put in place to reduce or control for the possibility of recall bias associated with

retrospective assessments, and to minimise the likelihood of investigator bias. First, researchers who administered this interview underwent intensive training, to acquire expertise in administering the interviews and to recognise the minimum amount of information required to make ratings, so as not to prolong the interview for the participant longer than needed. Second, all ratings were made by two researchers, and weekly consensus meetings, in which researchers rated interviews together, were held and attended by all researchers conducting the interview. Third and last, the researchers were unaware of case-control status whilst interviewing and rating, and this was important to reduce the possibility of investigator bias, as well as to increase inter-rater reliability. In this thesis I focused on the experience of physical and sexual abuse, which have been defined below.

Physical abuse

Physical abuse was considered to be any event of violence towards the individual by an adult or older sibling in the household, which occurred before the age of 17 years. Positive responses to screening questions were followed up by more detailed questions regarding the perpetrator, the method (e.g. with a hand, belt or stick), and the nature of injuries sustained. These questions were repeated for each perpetrator, and for any period of abuse that differed in the level of severity.

Sexual Abuse

Sexual abuse was defined as any unwanted sexual experience with an adult (within or outside the family) or peer that occurred before the age of 17 years. The section begins with four screening questions, which aim to elicit the same answers, but are comprised of different wording. This is due to the fact that some individuals may blame themselves for the abuse (Finkelhor et al., 1986), and therefore may not identify with words such as 'unwanted' or 'against your wishes'. Questions were repeated for each abuse by a different perpetrator, or for changes in severity over time.

For all of the above adversities, information were collected on frequency of the adversity (0 'never', 1 'rarely – once or twice', 2 'occasionally – more than twice, less than monthly', 3 'frequently – monthly or more', 4 'very frequently – weekly or more'), as well as on the age at which it started and ended, and the duration in months. Severity of psychological, physical, and sexual abuse was rated on a four-point scale: 0 (none), 1 (some), 2 (moderate), 3 (marked). In contrast, severity of household discord was rated on a five-point scale: 0 (none), 1 (some), 2 (moderate), 3 (marked), and 4 (violence). In addition, the perpetrator of abuse (or family arrangement for Household Discord) was recorded: (1 'both parents', 2 'mother', 3 'father', 4 'sibling', 5 'other relative', 6 'family friend', or 7 'other person in household', in addition to report of contact with official services (0 'none', 1 'social services', 2 'GP', 3 'police', 4 'other').

The final score for both physical and sexual abuse can range from 0 to 3 (0 = no abuse, 1 = mild level of abuse, 2 = moderate level of abuse and 3 = severe level of abuse). All participants in the study are assigned to one of the four groups according to the level of the severity of the abuse experienced. As it is unfortunately quite common to find reports of exposure to both physical and sexual abuse in the same individual; when both physical and sexual abuse occurred, the participant was included in the group of the most severe experience (e.g. a participant with physical moderate abuse and severe sexual abuse was included in the group severe abuse) (Suliman et al., 2009). When there was uncertainty on the classification of the individuals because of missing data (e.g. a participant reported mild level of physical abuse and information about the sexual abuse was not available), the participant was excluded from the analysis (n=3). Similarly, when participants reported a history of no trauma in one modality of abuse (e.g. physical abuse) and information was missing for the others (e.g. sexual abuse), they were excluded from the analyses.

2.1.4.3 Clinical features of the patients

The clinical characteristics of the patients were evaluated in terms of symptoms severity, diagnosis, time between the onset of psychosis and the presentation to mental health services (Duration of Untreated Psychosis) and total exposure to antipsychotic medications.

2.1.4.3.1 Positive and Negative Syndrome Scale (PANSS)

Symptom severity was assessed in a clinical interview using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987). The PANSS, a widely adopted and well validated instrument, comprises 30 items corresponding to 30 different symptoms, each with a possible rating ranging from 1 to 7 (1 = Absent, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Moderate-Severe, 6 = Severe, 7 = Extreme) (Oord et al. 2006). The scoring was established on the basis of the information obtained during the assessment. Researchers who administered the PANSS underwent specific training, to acquire expertise in administering the interviews, to recognise the minimum amount of information required to make ratings and to score the items with high inter-rater reliability ($\kappa = 0.8$). The PANSS items can be grouped in three categories: “Positive Symptoms” (7 items), “Negative Symptoms” (7 items) and “General Psychopathology” (16 items), with a maximum total score of 210. Cut offs can be introduced to estimate the clinical severity of the presentation. Individuals can be considered mildly ill with a total score of 58, moderately ill with a total score of 75, markedly ill with a total score of 95 and severely ill with a total score of 116 or above (Leucht et al., 2005).

2.1.4.3.2 Diagnosis

Patients diagnoses were obtained using the Operational Criteria in Studies of Psychotic Illness (OPCRIT). OPCRIT is a development and expansion of the OPCRIT checklist designed to facilitate a polydiagnostic approach to mental illness and validated by Craddock et al. (1996) (McGuffin et al., 1991). The items contained within the checklist allow classification of subjects according to the functional psychosis and affective disorder categories in DSM-IV, DSM-III, DSM-III-R, ICD-10 research criteria, the St. Louis criteria, the Research Diagnostic Criteria and the criteria of Taylor and Abrams (Feighner et al. 1972; Spitzer et al. 1978) (Rutter and Shaffer 1980; American Psychiatric Association 2000; World Health Organization 1992). OPCRIT also allows a diagnosis of schizophrenia to be made according to the 'flexible' criteria of Carpenter et al. (1976), and the first rank symptoms of Schneider (Spitzer et al. 1978). Where appropriate, a classification into schizophrenia subtypes is made using the systems of Tsuang and Winokur, and Crow and Farmer (Tsuang and Winokur 1974; Crow 1980; Farmer et al. 1983). In this thesis I used the diagnostic categories of the DSM-IV⁸. Information was obtained from the first time any psychotic symptoms were experienced for more than one week, until a month after the first contact with psychiatric services, consulting the patients' case notes. In cases of diagnostic uncertainty this period was extended for further three months (n = 23 patients). All diagnoses were performed by qualified psychiatrists, subject to comprehensive training and inter-rater reliability testing (kappa = 0.9).

⁸ The diagnoses used in this thesis are virtually unchanged from DSM-IV to DSM-V. The revision of the criteria concerned elements that does not affect the key elements of the disorders (e.g. elimination of the schizophrenia subtypes, dimensional approach to the ratings of the core symptoms, elimination of the importance of bizarre delusions in schizophrenia and delusion disorder) (American Psychiatric Association 2013; Regier et al. 2013).

2.1.4.3.3 Duration of Untreated Psychosis (DUP)

The time between the onset of psychosis and the presentation to mental health services was quantified as Duration of Untreated Psychosis (DUP) and measured using the Nottingham Onset Schedule (NOS) (Singh et al. 2005). This questionnaire was completed with information obtained from the patients via interview, in addition to those obtained from their clinical notes. The DUP was calculated from the first time any psychotic symptoms were experienced for more than one week, until the patient presented to services. The NOS provides a standardised and reliable way of recording early changes in psychotic symptoms and it has shown to have a high degree of inter-rater and test-retest reliability for all components (Singh et al. 2005). Researchers who completed the NOS were appropriately trained to ensure consistency and high levels of inter-rater reliability ($\kappa = 0.8$). For this thesis I focused on the time period between first symptoms and start of treatment, which included the prodromal phase but did not account for any potential brief limited intermittent psychotic symptoms (BLIPS) prior to this time (Singh et al., 2005).

2.1.4.3.4 Exposure to antipsychotic medication

Detailed information on antipsychotic and other medications prescribed were obtained from clinical notes. Antipsychotic medications are known to have an effect on cortisol levels, particularly on cortisol production during the day and on cortical and subcortical brain volumes and therefore this information was used to account for the effect of different treatments across participants (Dazzan et al. 2005; Navari and Dazzan 2009; Mondelli et al. 2010). Data were collected on type of antipsychotics, dose and length of

exposure, from the first prescription to the cortisol evaluation. The total chlorpromazine-equivalent dose was calculated by summing all daily doses from the first day of treatment with antipsychotics up to the collection of saliva samples (Atkins et al. 1997; Woods 2003). The total antipsychotic amount prescribed was then converted to chlorpromazine equivalents to make it comparable across subjects according to defined criteria (Atkins et al 1997; Woods, 2003).

2.1.5 Statistical analyses – socio-demographic and clinical data

All analyses were performed using the Statistical Package for the Social Sciences (SPSS Version 22.0). Inferential statistics were performed on socio-demographic, clinical and abuse exposure data to describe the characteristics of the sample.

2.1.5.1 Socio-demographic and trauma exposure descriptive

Socio-demographic and trauma exposure differences between cases and healthy controls were compared using an independent samples t-test, one-way analysis of variance (ANOVA), or chi-square test, as appropriate.

2.1.5.2 Clinical data and trauma exposure

In order to estimate the relationship between trauma exposure and different levels of clinical severity, symptoms were grouped in three categories: “Positive Symptoms”, “Negative Symptoms” and “General

Psychopathology”, following the PANSS classification. Mean scores for each of these symptom group were compared between individuals with and without abuse exposure using an independent samples t-test (Kay et al. 1987). In a second step, severity of abuse was taken into consideration and the mean scores for each symptom group (i.e. Positive Symptoms, Negative Symptoms and General Psychopathology) were compared across patients with different degrees of childhood abuse (i.e. no abuse, mild, moderate and severe abuse exposure) using two-way analysis of variance (ANOVA). Finally, the PANSS scores were divided into groups and ordered in terms of severity of illness as defined by Leucht and colleagues. This grouping was used to explore the relationship between global symptom severity (mildly ill with a PANSS total score of 58, moderately ill with a PANSS of 75, markedly ill with a PANSS of 95 and severely ill with a PANSS of 116 or above) (Leucht et al., 2005) and abuse exposure. Two-way analysis of variance (ANOVA) was used to assess the distribution of severity of trauma exposure across the four groups.

2.2 Structural MRI methodology

The effect of childhood abuse on brain structure was investigated in terms of regional grey matter volume and cortical thickness in cases and controls, with and without abuse exposure. This section describes the image acquisition, pre-processing of the MRI images and the statistical analyses used.

2.2.1 Acquisition of Structural MRI data

All structural MRI data were acquired using a 3-Tesla GE Signa HDx MR System at the Centre of Neuroimaging Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London. For all scans an 8-channel head coil was used and head movement was limited by foam padding within the head coil. The structural scan acquired from each subject was a 3D T1-weighted, MPRAGE (magnetization-prepared rapid gradient-echo) volumetric scan in the sagittal orientation. The MPRAGE image has an image matrix size = 256x256x166, with in-plane voxel size = 1.02x1.02mm, slice thickness = 1.2 mm, echo time = 2.848ms repetition time = 6.988ms, inversion time = 650 ms, flip angle = 20°, one data average. The total acquisition time was 10 minutes.

2.2.2 Initial processing of structural images

After acquisition, the images were checked for quality, movement and other artefacts using Statistical Parametric Mapping version 8 release 5263 (SPM-8-5263) (www.fil.ion.ucl.ac.uk/spm/software/spm8/), which is a widely used neuroimaging software package. The presence of artefacts was noted and used to

inform subsequent analyses. The level of artefacts was graded on a scale from 1 to 3. Eight scans with a score of 2.5 or above were excluded from subsequent analyses. All images were re-oriented along the anterior and posterior commissures (AC-PC) line. The reorientation was automatically obtained and the outputs manually checked following the AC-PC line using <http://imaging.mrc-cbu.cam.ac.uk/imaging/FindingCommissures> as a guidance tool (<https://www.jiscmail.ac.uk/cgi-bin/wa.exe?A2=spm;5819d056.0810>). Manual corrections of orientation were made when necessary.

2.2.3 Coding of childhood exposure for structural MRI analysis

Irrespective of whether the measure of interest is either grey matter volume or cortical thickness, the power to detect structural abnormalities across groups is a function of group size (Lüders et al. 2002; Pell et al. 2008; Barnes et al. 2010). Indeed in the presence of groups of small sample size, the power of the model decreases significantly reducing the possibility of detecting a true effect (type II error), in addition a small sample size also increases the chance that a significant result is not a true effect (type I error) (Button et al., 2013). Within the neuroimaging field a group with less than 16 participants is generally considered too small to have sufficient power to yield reliable results. (Pell et al. 2008; Friston 2012). In my study the severity of abuse ranged between no abuse, mild, moderate and severe. Using the abuse exposure as a categorical variable with 4 levels (i.e. no abuse, mild, moderate and severe abuse) would have dramatically reduced the size of the groups of the individuals exposed to mild, moderate, severe abuse, especially among controls, limiting the strength of the results. Therefore I decided to use the exposure to childhood abuse as a dichotomous variable; participants with exposure to physical and sexual abuse in childhood comprise individuals with moderate to severe level of abuse. Moderate and severe abuse are considered to describe a significant exposure to either physical or sexual abuse unlike mild abuse (Bifulco et al., 2005). In contrast with moderate or severe abuse, mild abuse does not imply

touching by the perpetrator, in cases of sexual abuse, nor physical consequences (e.g. bruises, injuries requiring medical attention) in case of physical abuse. Significant abuse exposure is considered more likely to be associated with biological consequences therefore in line with other studies exploring the effect of childhood abuse, I decided to focus on this category of abuse and to exclude the individuals exposed to mild childhood abuse (7 controls and 9 cases) (Klaassens et al. 2009; Carpenter et al. 2011; Lu et al. 2013). Furthermore, in order to increase the total number of healthy controls with a history of exposure to physical or sexual abuse, and to have numerically balanced groups for the analysis, healthy individuals with these characteristics that were already contacted by the Wellcome Trust study on Childhood Trauma and Psychosis, and the longitudinal BRC Psychosis Theme study on Genetics and Psychosis in the study (but without an MRI scan) were specifically offered to undergo an MRI scan. To conclude, in terms of abuse exposure, the sample I used was composed by a total of 160 individuals: 81 individuals without abuse exposure (34 controls and 47 cases) and 79 individuals with a history of childhood abuse (30 controls and 49 cases). Among the controls positive for abuse, 15 had a moderate level of abuse and 15 had a severe level of abuse; among cases, there were 18 with moderate level of abuse and 31 with severe level of abuse.

2.2.4 Structural MRI: Grey Matter Volume

SPM-12-2015 (www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to pre-process and statistically analyse the images. SPM-12 was chosen as it has a number of advantages for accurate segmentation of structural imaging data. Ideally one should only use a single version of SPM when processing data, however SPM8 in section 2.2.2 was simply used for checking data quality and reorienting scans. SPM allows researchers to study focal volumetric differences across the whole brain in a selected tissue (i.e. grey matter), and is particularly appropriate in the case of a disease or stressors such as psychosis and

childhood abuse which are thought to be characterised by neuroanatomical abnormalities spatially distributed across the brain (Mourao-Miranda et al. 2012; Herman 2013). After pre-processing the data by automatically segmenting the images into regional volumes of tissue (i.e. grey matter), the software produces a map at the voxel level of statistically significant differences between groups (i.e. cases and controls with and without history of physical and sexual abuse) using the General Linear Model (GLM).

2.2.4.1 SPM Pre-processing

The overall aim of the pre-processing step is to eliminate differences across images originated from global brain shape, movements and orientation in the scanner and to prepare the data for statistical analysis. Initially, images were segmented, rigidly oriented with the MNI template through an iterative process that normalises them to a template (using least-squares analysis) and segments (into grey matter, white matter, CSF, bone, soft tissue and air/background maps) the images at the same time. In SPM-12-2015 this is obtained with the “New Segmentation” command, an extension of the “Universal Segmentation” command used in previous version of SPM where the normalisation, segmentation and bias field correction are conducted in one model. The following step, the Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL), was used to obtain a nonlinear image registration allowing for an optimised data processing pipeline (Ashburner, 2010). The DARTEL procedure improves both the sensitivity and the localisation of VBM studies by registering subjects’ structural images to a custom template derived from the individuals images themselves. The inter-subject registration process uses an initial template obtained from a mean of all the subjects’ images, using parameters from the spatial transformation and segmentation in the previous step. Deformations from this template to each individual image, known as ‘flow-fields’, are then computed. The inverse of the flow-fields were applied to each image to re-generate the template. This procedure was repeated 6 times for all

2.2.4.2 Pre-processing quality control

In order to assess the quality of the data and check for any outlier, values of grey matter, white matter, CSF volumes were automatically extracted using SPM-12-2015 and total intracranial volumes (TIV) were calculated. To identify potential outliers, these values were then correlated with age and gender to explore whether values were within the expected normal pattern of development, which is characterised by larger TIV in male individuals than females and by a reduction of grey matter volume with age (Lüders et al. 2002; Sowell et al. 2003).

2.2.4.3 Statistical Analyses – Grey matter volume

2.2.4.3.1 Regional brain volumes analysis

2.2.4.3.1.1 Effect of physical and sexual abuse on grey matter volume in individuals with and without psychosis

A DARTEL based VBM analysis was conducted to investigate brain-wide grey matter volume differences between groups (case vs control; having a history of physical and sexual abuse in childhood vs not having such a history). Two-way analysis of covariance (ANCOVA) was performed in SPM-12-2015. As the grey matter volume is negatively correlated with aging and positively correlated with head

size, to account for these confounders age at MRI and TIV were included as covariates of no-interest in the model (Lüders et al. 2002; Sowell et al. 2003). The impact of ethnic variations on the neuroanatomical characteristics of psychosis has been minimally studied, but recent research has shown that individuals with schizophrenia from different ethnic background show both similar and distinct changes in brain structure compared to matched controls (Gong et al., 2015). Thus, I included the ethnic origin of the participants as a covariate of no interest in the analysis. As among individuals of ethnic origins other than white the differences in grey matter volume were of a small magnitude, I coded the variables as dichotomous (participants of white ethnicity vs participants of any other ethnical background).

Summary: Model 1a (Entire sample).

Variables of interest: Diagnosis (Psychosis/Control), Physical & Sexual Abuse (yes/no).

Covariates of no interest: Age, TIV, Ethnicity (white/other).

Sample composition: 160 participants: 81 individuals without abuse exposure (34 controls and 47 cases) and 79 individuals with history of childhood abuse (30 controls and 49 cases).

2.2.4.3.1.2 Patients only: Differences in grey matter volume with and without a history of childhood abuse

Grey matter volume abnormalities are consistently reported between FEP and healthy controls in frontal limbic and parietal areas as well as in regions related to the stress response as the hippocampus (Fornito et al. 2009; Fusar-Poli et al. 2012). As the effect of abuse exposure in childhood has been reported in similar brain regions, the variance due to psychosis might reduce the likelihood of identifying a significant effect associated with abuse. Indeed the effect of abuse exposure may have a smaller effect size than the effect of psychosis or result in abnormalities, which may be the opposite than those due to gender. I explored

the impact of abuse in cases only, with and without history of childhood abuse (Martin H. Teicher et al., 2006). In order to increase the sensitivity and the localisation of this analysis, a specific DARTEL template for this sub-group (cases with and without abuse exposure) was created and the pre-processing was executed again as described in the section 2.2.4.1. A one-way analysis of covariance (ANCOVA) was performed in SPM-12-2015 with age, ethnicity and TIV included as covariates of no-interest in the model.

Summary Model: 2a (Cases only).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 96 individuals (47 cases without abuse exposure and 49 cases with history of childhood abuse).

2.2.4.3.1.3 Controls only: Differences in grey matter volume in people with and without a history of childhood abuse

Similarly I investigated differences in grey matter volume voxel-wise in controls with or without history of childhood physical and sexual abuse with a DARTEL based VBM analysis. Also for this analysis a specific DARTEL template (controls with and without abuse exposure) was created and the new pre-processing was ran as described in the section 2.2.4.1. A one-way analysis of covariance (ANCOVA) was performed in SPM-12-2015 with age, ethnicity and TIV included as covariates of no-interest in the model.

Summary Model: 3a (Controls only).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 64 individuals (30 controls without abuse exposure and 34 controls with history of childhood abuse).

2.2.4.3.1.4 Gender modulation of the effect of physical and sexual abuse on grey matter volume in individuals with and without psychosis

Gender differences in brain morphology have been consistently reported. More specifically, healthy women appear to have greater grey matter volume, cortical thickness, gyrifications and more complex cortical structures of the temporal and frontal lobes than healthy men when total intracranial volume is adjusted for (Courten-Myers 1999; Rabinowicz et al. 1999; Luders et al. 2004; Gur et al. 2004; Im et al. 2006; Luders et al. 2006; Takahashi et al. 2011). Furthermore, these effects of gender have also been reported in individuals with first episode psychosis, particularly in brain structures associated with the stress response such as smaller left hippocampus in male FEP (Pruessner et al. 2015). As the effect of abuse exposure may have a smaller effect size than the effect of gender or result in abnormalities, which may be the opposite than those due to gender, investigating the effect of abuse in males and females separately may be an advantage. Therefore, I conducted a set of exploratory analyses to investigate the effect of abuse on grey matter abnormalities in men and women separately. In order to increase the sensitivity and the localisation of this analysis specific DARTEL templates for these sub-groups (i.e. male cases and controls with and without abuse exposure and female cases and controls with and without abuse exposure) were created and the pre-processing was executed again as described in the section 2.2.4.1.

2.2.4.3.1.4.1 Gender differences in grey matter volume in patients and controls with and without a history of childhood abuse

Similarly to what I conducted for the entire sample, I investigated differences in regional grey matter volume in cases and controls with or without history of childhood physical and sexual abuse in male and female participants separately with a DARTEL based VBM analysis. I performed a two-way analysis of covariance (ANCOVA) with age TIV and ethnicity as covariates of no interests in SPM-12-2015.

Summary: Model 1b (Female only sample).

Variables of interest: Diagnosis (Psychosis/Control), Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 69 participants: 34 individuals without abuse exposure (20 controls and 14 cases) and 35 individuals with history of childhood abuse (15 controls and 20 cases).

Summary: Model 1c (Male only sample).

Variables of interest: Diagnosis (Psychosis/Control), Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 92 participants: 48 individuals without abuse exposure (14 controls and 34 cases) and 44 individuals with history of childhood abuse (15 controls and 29 cases).

2.2.4.3.1.4.2 Gender differences in grey matter volume in cases with and without a history of childhood abuse

I then explored differences in grey matter volume across the whole brain in cases exposed and not exposed to physical and sexual abuse in male and female participants separately with another DARTEL

based VBM analysis. Also for this analysis specific DARTEL templates (i.e. male cases with and without abuse exposure and female cases with and without abuse exposure) were created and the new pre-processing was ran as described in the section 2.2.4.1. A one-way analysis of covariance (ANCOVA) was performed in SPM-12-2015 with age, ethnicity and TIV included as covariates of no-interest in the model.

Summary: Model 2b (Female patients only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 34 participants (14 cases without abuse exposure and 20 cases with history of childhood abuse).

Summary: Model 2c (Male patients only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 63 participants (34 cases without abuse exposure and 29 cases with history of childhood abuse).

2.2.4.1.4.3 Gender differences in grey matter volume in controls with and without a history of childhood abuse

Finally I investigated differences in grey matter volume across the whole brain in controls exposed and not exposed to physical and sexual abuse in male and female participants separately, with a DARTEL based VBM analysis. Also for this analysis specific DARTEL templates (i.e. male controls with and

without abuse exposure and female controls with and without abuse exposure) were created and the new pre-processing was ran as described in the section 2.2.4.1. A one-way analysis of covariance (ANCOVA) was performed in SPM-12-2015 with age, ethnicity and TIV included as covariates of no-interest in the model.

Summary: Model 3b (Female controls only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 35 participants (20 controls without abuse exposure and 15 controls with history of childhood abuse).

Summary: Model 3c (Male controls only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, TIV, Ethnicity (White/Other).

Sample composition: 29 participants (14 controls without abuse exposure and 15 controls with history of childhood abuse).

2.2.4.3.2 Region of interest analysis

SPM allows a-priori hypotheses to be tested by looking for group differences in specific areas of the brain. With the use of image masks, it is possible to apply the standard voxel level statistics (e.g. Family Wise Error or False Discovery Rate) only on a specific region of interest (ROI) instead of brain-wise. In SPM the mask is applied using an option named “Small Volume Correction (SVC)”. I used this option to investigate whether the regions most consistently associated with trauma exposure in childhood were also

significantly different between groups in my sample. The meta-analysis by Lim et al. (2014) provide the most recent and comprehensive evidence for grey matter changes in healthy controls exposed to childhood maltreatment I investigated all the 15 areas for which there was an effect of childhood maltreatment on regional brain volume in healthy controls (Lim et al. (2014)). I examined the same regions in my sample of individuals with and without abuse exposure, irrespective of presence of psychosis. Unfortunately there are no published meta-analyses investigating the specific effects of physical and sexual abuse. Therefore, I selected the results from this meta-analysis that used a cumulative measure of childhood maltreatment (Lim et al. 2014). The ROIs Lim et al. (2014) were identified as Brodmann areas and each ROI mask was created using WFUpickatlas as part of the SPM-12-2015. The mask was applied to the data using the Small Volume Correction (SVC) option of SPM-12-2015.

Summary: ROIs abuse (Entire sample).

Variables of interest: Physical & Sexual Abuse (yes/no).

Covariates of no interest: Age, TIV, Ethnicity (white/other).

Sample composition: 160 participants: 81 individuals without abuse exposure and 79 individuals with history of childhood abuse.

Areas of interest: Regions from Lim et al. (2014).

2.2.4.3.3 Reporting results for VBM analysis

Neuroimaging data are characterised by high level of inter subject variability and proportionally lower level of intra subject variability (Thirion et al., 2007). This characteristic, in combination with the inherently high number of comparisons which characterised each neuroimaging model, impact highly on

the sensitivity of the analysis therefore the possibility of finding results expressing a true effect (Wei et al., 2004). As a neuroimaging analysis can yield a high number of false positives (type I error) even if the probability is set at a relatively low value (i.e. $p < 0.001$), results are usually corrected for multiple comparisons (Friston et al. 1994). Identifying a true effect is a balance between sensitivity and specificity, correcting for multiple comparisons has proven a too stringent approach as it increases the type II error thus leads to the rejection of true results (Friston et al. 1994; Worsley 2003; Hayasaka and Nichols 2004). A combination of cluster extension and probability threshold height has been identified as a good compromise between the necessity of controlling for false positives and false negative (Friston et al. 1994; Worsley 2003; Hayasaka and Nichols 2004). The probability, just based on random chance, of adjacent voxels (cluster) being above a statistical threshold decreases with the increase of the cluster size, setting a combination of large enough cluster along with an appropriately small probability threshold can increase the sensitivity of the results without incurring in the too conservative approach of the multiple comparison correction (Friston et al. 1994; Worsley 2003; Hayasaka and Nichols 2004). A cluster size of at least 100 voxels cluster along with a threshold height of $p < 0.001$ is a reliable combination to guard against the type I error while reducing the type II error (Friston et al. 1994; Worsley 2003; Hayasaka and Nichols 2004). This combination has been widely used to identify effect sizes not strong enough to survive the correction for multiple comparisons but too big to be discarded as just occurring by random chance (Friston et al. 1994; Hayasaka and Nichols 2004; Thirion et al. 2007). In all VBM analyses, an initial statistical threshold height was set at $p < 0.001$ uncorrected with a minimum cluster size of 100 voxels. The second statistical threshold used was corrected for multiple comparisons (Family-wise Error FWE) for the whole brain with a significance threshold set at $p < 0.05$. The results were reported when significant at $p < 0.05$ FWE, or at $p < 0.001$ uncorrected with a minimum cluster size of 100 voxels when they did not survive the more conservative FWE correction (for each result the threshold is reported). When smoothing is applied to VBM data the resulting smoothness of the image maybe non-uniform (non-isotropic) and for VBM data this influences cluster sizes (with larger and more significant clusters more likely to appear in smoother areas) and this can bias the statistical estimations (Ashburner and Friston

2000; Hayasaka et al. 2004). To prevent this known effect all cluster level statistics were reported using Non-Stationary Cluster Extent Correction, which amends the cluster size and statistical significance according to the local smoothness values (Hayasaka et al., 2004).

2.2.5 Structural MRI: Cortical thickness

FreeSurfer is a set of tools for the analysis and visualisation of structural and functional brain imaging data (<http://freesurfer.net/fswiki>). FreeSurfer allows evaluation of local differences across the whole brain in terms of the cortical surface. Using the General Linear Model (GLM), FreeSurfer allows the user to test statistical models of how the cortical surface may change as a consequence of different parameters (i.e. having psychosis and being exposed to physical and sexual abuse). Initially, images are reconstructed with a fully automated process to create statistical maps of different brain characteristics (e.g. cortical thickness, cortical surface area), which would then be used to identify and compute real differences across participants. FreeSurfer version 5.1.0 was used to analyse the data.

2.2.5.1 FreeSurfer reconstruction

The FreeSurfer pipeline, activated with the command line “recon-all”, uses an automated algorithm to perform user-independent cortical reconstruction and subcortical volumetric segmentation, including the removal of non-brain tissue (skull, eyeballs and skin). The reconstruction pipeline consists of several stages. First, the image is registered with the Talairach atlas. After the skull is stripped, white matter and deep grey matter structures are segmented. Voxels are classified as being white matter or something other than white matter based on their intensity and the characteristics of the tissues around them (neighbour constraints). After the separation of the hemispheres and the removal of the cerebellum and brain stem based on the expected shape of these structures, the initial surface of the outer boundary of the white matter is generated. This surface is then refined to follow the intensity gradients between the white and grey matter (white matter surface). The pial surface is subsequently generated by following the intensity

gradients between grey matter and CSF. This is followed by intensity normalisation, tessellation of the grey matter-white matter boundary and the grey matter-CSF boundary, and automated topology correction. The transition point from one tissue to another (e.g. grey/white, grey/cerebrospinal) is optimally placed by determining the maximal shift in voxel intensity. The distance between the white matter and the pial surfaces gives the thickness at each location of cortex. After the reconstruction, thickness, local curvature, surface area, can also be computed (Fischl et al. 1999a; Fischl et al. 1999b; Fischl and Dale 2000) (see Figure 2.3 for visual representation). The FreeSurfer estimation of cortical thickness has been validated against histological and manual measurement of the cortices including individuals with schizophrenia (Rosas et al. 2002; Kuperberg et al. 2003; Salat 2004).

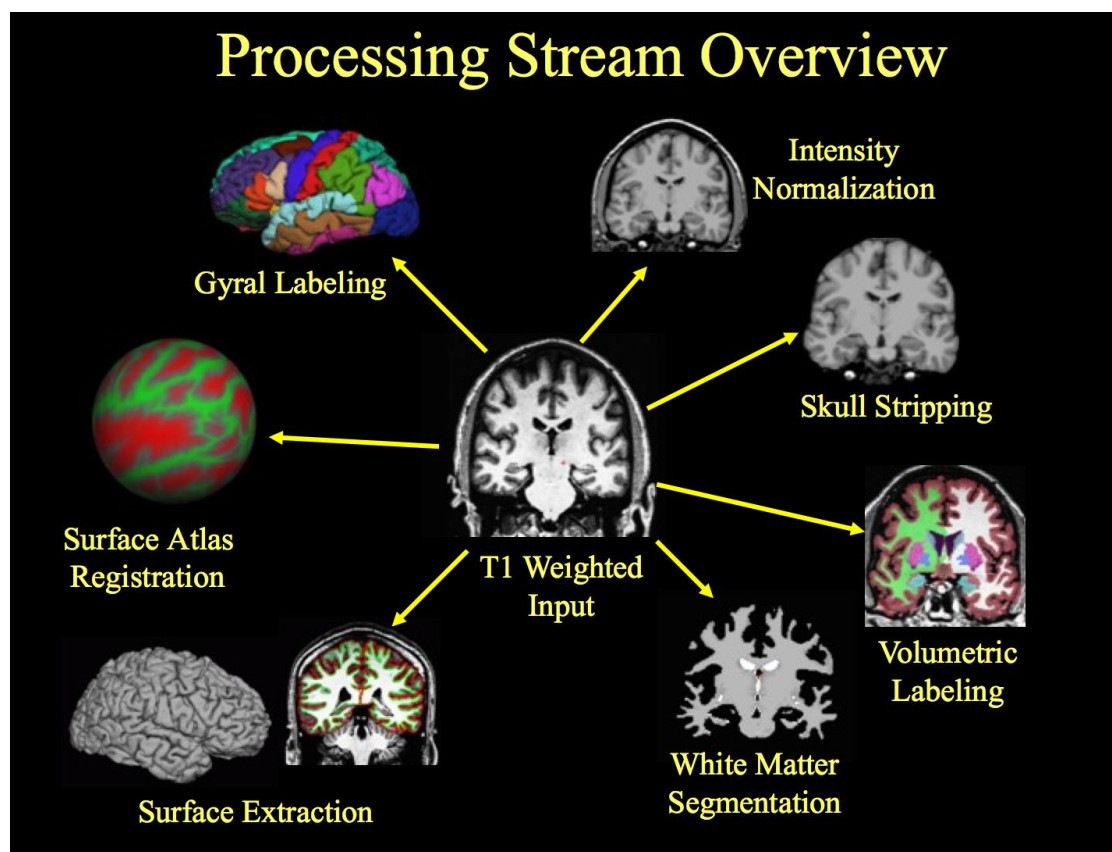


Figure 2.3: FreeSurfer reconstruction overview (modified by surfer.nmr.mgh.harvard.edu).

2.2.5.2 Pre-Processing quality control

In order to assess the quality of the reconstruction each image was checked manually, corrections were applied when necessary according the Freesurfer guidelines (<http://freesurfer.net/fswiki/FsTutorial/TroubleshootingData>), the reconstruction algorithm ran and the quality of the reconstruction was examined again. When the quality of the reconstruction was not satisfactory further corrections were applied and the reconstruction algorithm ran one last time. One reconstruction (the left hemisphere of one participant) was judged of insufficient quality after this additional step and it was excluded from the analysis. In order to evaluate the presence of any outliers, values of global cortical thickness were extracted using FreeSurfer and plotted against age and gender to compare them with the normal pattern of development (i.e. grey matter greater in male than female and reducing with age) (Lüders et al. 2002; Sowell et al. 2003).

2.2.5.3 Statistical analyses – Cortical thickness

The statistical analyses were conducted using Query, Design, Estimate Contrast (QDEC) interface, an application included with the FreeSurfer software package. A two-way ANOVA GLM for analysing differences in cortical thickness as a consequence of being a case or control and having or not having been exposed to childhood abuse was computed vertex-by-vertex in each hemisphere separately. QDEC employs two methods for automatically creating a design matrix. In the first one it is assumed that the exposure of interest (e.g. abuse history during childhood) has the same effect on one or more different morphometric measures of interest (e.g. thickness) between groups (e.g. being either case or control). This model implies that the two lines describing the variation of the morphometric measure (e.g. cortical thickness) in consequence of the presence of exposure (e.g. abuse history during childhood) have the

same slope for both groups (i.e. being either case or control) but have different intercept; this model is called Different Offset Same Slope (DOSS). The second possibility assumes that the exposure of interest (e.g. abuse history during childhood) has a different effect on one or more different morphometric measures of interest (e.g. thickness) in each group (e.g. being either case or control). Therefore the lines describing the variation of the morphometric measure (e.g. cortical thickness) as result of the presence of exposure (e.g. abuse history during childhood) have a different slope in each group (e.g. being either case or control) and different intercept; this model is called Different Offset Different Slope (DODS). Since the effect of abuse on cortical thickness may be different for cases and controls, the DODS was used. The DODS analysis is ran for each hemisphere separately. Cortical maps were smoothed using a 10 mm full width at half maximum (FWHM) Gaussian kernel and the results were visualised by overlaying significant cortical areas onto semi-inflated cortical surfaces.

2.2.5.3.1 Regional brain cortical thickness (vertex-wise)

2.2.5.3.1.1 Effect of physical and sexual abuse on cortical thickness in individuals with and without psychosis

A vertex-by-vertex DODS two-way analysis of covariance (ANCOVA) was performed in FreeSurfer 5.1.0 to investigate differences in cortical thickness across groups as consequence of being a case or a control, and having or not having a history of physical and sexual abuse in childhood. As the cortical thickness is negatively correlated with aging and positively correlated with head size, to account for these confounders age at MRI and global cortical thickness were included as covariates of no-interest in the model (Lüders et al. 2002; Sowell et al. 2003).

Summary: Model 1d (Entire sample).

Variables of interest: Diagnosis (Psychosis/Control), Physical & Sexual Abuse (yes/no).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 160 participants: 81 individuals without abuse exposure (34 controls and 47 cases) and 79 individuals with history of childhood abuse (30 controls and 49 cases); sample composition left hemisphere 159 participants: 80 individuals without abuse exposure (33 controls and 47 cases) and 79 individuals with history of childhood abuse (30 controls and 49 cases);

2.2.5.3.1.2 Patients only: Differences in cortical thickness in people with and without a history of childhood abuse

Cortical thickness differences abnormalities are consistently reported between FEP and healthy controls in frontal, limbic and parietal areas regions equally known to be affected by exposure to childhood (Hart and Rubia 2012; Xiao et al. 2015). Investigating the effect of abuse in cases alone may be an opportunity to detect abnormalities otherwise difficult to distinguish. I then investigated differences in cortical thickness vertex-wise in cases exposed and not exposed to physical and sexual abuse with another DODS vertex-by-vertex analysis. A one-way analysis of covariance (ANCOVA) was performed in FreeSurfer 5.1.0 with age, and global cortical thickness included as covariates of no-interest in the model.

Summary Model: 2d (Cases only).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right and left hemisphere: 96 individuals (47 without abuse exposure and 49 with history of childhood abuse).

2.2.5.3.1.3 Controls only: Differences in cortical thickness in individuals with and without a history of childhood abuse

Similarly I explored differences in cortical thickness in controls with or without exposure to physical and sexual abuse in childhood with a DODS vertex-by-vertex analysis. A one-way analysis of covariance (ANCOVA) was performed in FreeSurfer 5.1.0 with age and global cortical thickness included as covariates of no-interest in the model.

Summary Model: 3d (Controls only).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 64 individuals (30 without abuse exposure and 34 with history of childhood abuse); sample composition left hemisphere: 63 individuals (29 without abuse exposure and 34 with history of childhood abuse).

2.2.5.3.1.4 Gender modulation of effect of physical and sexual abuse on cortical thickness in individuals with and without psychosis

As cortical thickness has been reported to be different between genders in the healthy population as well as in individuals with psychosis, investigating the effect of abuse in male and female separately could provide an opportunity to observe differences of otherwise reduced effect size in mixed-gender samples (Courten-Myers 1999; Rabinowicz et al. 1999; Luders et al. 2004; Gur et al. 2004; Im et al. 2006; Lenroot et al. 2007; Luders et al. 2006; Takahashi et al. 2011; Pruessner et al. 2015).

2.2.5.3.1.4.1 Gender Differences in cortical thickness in patients and controls with and without a history of childhood abuse

I investigated differences in cortical thickness vertex-wise in cases and controls with or without history of childhood physical and sexual abuse in male and female participants separately with a DODS vertex-by-vertex analysis. I performed a two-way analysis of covariance (ANCOVA) with age TIV and global cortical thickness as covariates of no interests in FreeSurfer 5.1.0.

Summary: Model 1e (Female only sample).

Variables of interest: Diagnosis (Psychosis/Control), Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere 69 participants: 34 individuals without abuse exposure (20 controls and 14 cases) and 35 individuals with history of childhood abuse (15 controls and 20 cases); sample composition left hemisphere: 68 participants: 33 individuals without abuse exposure (19 controls and 14 cases) and 35 individuals with history of childhood abuse (15 controls and 20 cases).

Summary: Model 1f (Male patients only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 92 participants: 48 individuals without abuse exposure (14 controls and 34 cases) and 44 individuals with history of childhood abuse (15 controls and 29 cases); sample composition left hemisphere: 92 participants: 48 individuals without abuse exposure (14 controls and 34 cases) and 44 individuals with history of childhood abuse (15 controls and 29 cases).

2.2.5.3.1.4.2 Gender differences in cortical thickness in cases with and without a history of childhood abuse

I then explored differences in cortical thickness vertex-wise in cases exposed and not exposed to physical and sexual abuse in male and female participants separately, with another DODS vertex-by-vertex analysis. A one-way analysis of covariance (ANCOVA) was performed in FreeSurfer 5.1.0 with age and global cortical thickness included as covariates of no-interest in the model.

Summary: Model 2e (Female patients only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 34 participants (14 cases without abuse exposure and 20 cases with history of childhood abuse); sample composition left hemisphere 63 participants (34 cases without abuse exposure and 29 cases with history of childhood abuse).

Summary: Model 2f (Male patients only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 63 participants (34 cases without abuse exposure and 29 cases with history of childhood abuse); sample composition left hemisphere: 63 participants (34 cases without abuse exposure and 29 cases with history of childhood abuse).

2.2.5.3.1.4.3 Gender differences in cortical thickness in controls with and without a history of childhood abuse

Finally, I explored differences in cortical thickness in controls exposed and not exposed to physical and sexual abuse in male and female participants separately with a DODS vertex-wise analysis. A one-way analysis of covariance (ANCOVA) was performed in FreeSurfer 5.1.0 with age, global cortical thickness as covariates of no-interest in the model.

Summary: Model 3e (Female controls only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 35 participants (20 controls without abuse exposure and 15 controls with history of childhood abuse); sample composition left hemisphere 34 participants (19 controls without abuse exposure and 15 controls with history of childhood abuse)

Summary: Model 3f (Male controls only sample).

Variables of interest: Physical & Sexual Abuse (Yes/No).

Covariates of no interest: Age, Global cortical thickness.

Sample composition right hemisphere: 29 participants (14 controls without abuse exposure and 15 controls with history of childhood abuse); sample composition left hemisphere 29 participants (14 controls without abuse exposure and 15 controls with history of childhood abuse).

2.2.5.3.2 Regions of interest analysis

As in the case of SPM, FreeSurfer allows for testing of a-priori hypotheses looking for group differences in specific areas of the brain. It is possible to apply the GLM (e.g. DODS ANCOVA) only on a specific region of interest (ROI) instead of vertex-wise using an ad hoc mask that selects only the vertices in that area. Unfortunately there are no meta-analyses describing the impact of abuse on cortical thickness that can be used to select a-priori areas to test for my hypotheses. I therefore decided to investigate whether abnormalities in either cortical surface or cortical thickness were present in the same areas that showed significant differences in the SPM ROI analyses in my sample. Grey matter volume is a function of both surface and thickness, this investigation is set to clarify whether the grey matter alterations identified from the ROIs would result from more structurally defined abnormalities in either cortical surface or cortical thickness. The ROIs showing significant results from the SPM ROI analyses were manually drawn in the FreeSurfer application QDEC using Talairach coordinates as point of reference and values for surface and thickness extracted with command-line. The computations were performed using t-test or ANOVA as appropriate on SPSS Version 22.0.

2.2.5.3.3 Reporting results for FreeSurfer analysis

A first explorative vertex-wise search was ran with statistical significance threshold set at $p < 0.001$ uncorrected for multiple comparison. The second statistical assessment of each hemisphere was corrected for multiple comparisons with permutation testing with Monte Carlo Simulation and cluster analysis, a

standard procedure implemented in FreeSurfer 5.1.0. The fundamental hypothesis of this approach is that random oscillation of cortical thickness differences are unlikely to cluster in space; thus the analysis is repeated 10,000 times with arbitrary group labels in order to generate a distribution under the null hypothesis of no difference between groups (Nichols and Holmes 2002; Pereira et al. 2012; Oertel-Knochel et al. 2013). This simulation yields the minimum cluster size for the comparison based on a probability threshold, in my case the p-value was set at <0.05 . The results were reported when significant at $p < 0.05$ after correction for multiple comparisons.

2.3 Hypothalamic-Pituitary-Adrenal (HPA) axis function methodology

Cortisol is the main stress hormone produced by the HPA axis. Measuring cortisol is a direct, reliable and well-replicated way to estimate the activity of the HPA axis, and therefore the capacity of the organism to adapt to stress. Cortisol levels in the saliva are in equilibrium with cortisol blood concentration, so that changes in the latter are mirrored by variations in the former. I investigated the impact of childhood trauma on HPA axis activity by measuring abnormalities in cortisol production at awakening, when there is a physiological increase in cortisol concentration. This represents a recognized measure of acute reactivity of the axis and is comparable to being exposed to a medium stressor. I also evaluated cortisol salivary concentration during the day, to estimate cortisol basal production (Dickerson and Kemeny, 2004).

2.3.1 Collection of saliva cortisol sample

During the study there was a change of protocol, which modified the way saliva cortisol samples were collected and analysed. Initially saliva samples were collected to measure salivary concentration, using a salivette device (Sarstedt, Leicester, UK) in which saliva is adsorbed in a cotton roll. To ensure a better patients' acceptability the collection of saliva samples was finally obtained using arrow-head-shaped hydrocellulose sponges attached to a shaft provided by salivette as well (Sarstedt, Leicester, UK). At study completion 36 % of saliva samples were collected using cotton rolls and 64% with arrow-head-shaped hydrocellulose sponges. The two methods are reported to have the same levels of reliability in collecting analysable samples (Shirtcliff, 2001). Subjects were instructed to collect saliva introducing the swab of the arrow in the mouth for two minutes at different time points during the day. The first one was

immediately after awakening (0 minutes) and then at 15, 30, 60 minutes after awakening. Again participants were asked to collect saliva samples at 12:00 pm and at 8:00 pm. Reflecting spontaneous variation in the circadian glucocorticoid oscillation, after 10:00 am there is a steady reduction in the cortisol hematic concentration to reach the lower level in the afternoon. Waking up after 10:00 am reduces the increase in cortisol, which characterises awakening. Thus participants were instructed to wake up before 10:00 am and collect the first sample when still in bed and then not to have breakfast or brush their teeth during the first hour after awakening. This instruction was repeated for the 30 minutes before taking the sample at 12:00 pm and 8:00 pm to prevent falsely high cortisol values due to plasma exudates from minor bleedings in the oral cavity or from meal-stimulated rises cortisol. During collection individuals were instructed not to touch the samples with their hands. At each time point the subjects were also advised to write down on provided “information sheets” the time of collection, if they had anything to eat or drink or any difficult or tense situation before collecting the sample. Participants were also asked about their use of medication, and if women about the phase of their period (a full copy of form with the instruction for the participants is in Appendix A for reference). Samples were kept in the refrigerator overnight and then collected by the researcher or sent back in the post the following morning. On arrival at the laboratory the samples were frozen at -20°C . After thawing saliva samples were centrifuged at 3000 rev/min for five minutes, which resulted in a clear supernatant of low viscosity. A 50 μl aliquot of saliva was used for duplicate analysis. The saliva cortisol concentrations were determined in two different ways depending on the change of protocol during the study: 36 % of the samples were analysed using the “Immucite” DPPC’s immunoassay analyser (www.diagnostic.siemens.com) and 64% with the High Sensitivity Salivary Cortisol ELISA KIT from Salimetrics following the recommended procedure. As the saliva samples were analysed from two different laboratories, in order to ensure the reliability of the two techniques in determining cortisol values, samples from ten subjects were used to calculate cortisol levels with both analytic methods. A linear regression model found very high correlation between the values obtained with these different techniques (z-scores; $r = 0.93$; slope = 0.88; intercept = 1.38; standardized coefficient = 0.93; $F = 15.1$; $p < 0.001$). Consequently before being

analysed the cortisol values were standardised converting them into in z-score⁹ (Belvederi et al., 2012).

The outliers were excluded prior to the conversion to z-score.

2.3.2 Quality control of cortisol data

Different procedures were put in place to assure the quality of the collection and protocol time restrains of the cortisol sample collection. Where time of collection was missing for one or more samples, the participant was contacted and the time of the sample collection (most approximate time) was checked. If after contacting the participant it was not possible to estimate the time of collection, the sample was excluded from further measurement. However, none on the sample was excluded for that reason. When the time sheet was missing and no information on time of sample collection could be obtained, the samples were excluded from measurements. Time of collection was confirmed for all saliva samples. In participants in whom the first sample after awakening (0 minutes) was taken after 10:00, the saliva samples for that participant were excluded from the study dataset. However, none on the samples were excluded for that reason. When samples were not collected exactly at the expected time, the data were included if the sample was taken within the following range: for 15 minutes sample ± 5 min; for 30 minutes sample ± 10 min; for 60 minutes sample ± 15 min; for 12 noon sample and 8 pm sample ± 1 hr. None of the samples were collected outside these intervals.

Cortisol values were checked for outliers that were then excluded from the analysis. The outliers were defined as those participants who have their cortisol values deviating more than two standard deviations from the mean value of the group they belong to.

⁹ A z-score is a statistical measurement of a score's relationship to the mean in a group of scores. A z-score is the number of standard deviations an observation is above or below the mean.

2.3.3. Medication Exposure and Hypothalamic-pituitary-adrenal and analysis

As antipsychotic medications are thought to affect cortisol levels, in order to evaluate whether there was a difference in cumulative antipsychotic exposure between individuals with and without history of childhood abuse, total chlorpromazine-equivalent dose was calculated and compared across the different levels of trauma using independent samples T-test or one-way analysis of variance (ANOVA) as appropriate (Woods 2003; Taylor et al. 2009). If there was a significant difference in chlorpromazine equivalents between groups, these were added as covariates to the analyses exploring the impact of childhood abuse on the HPA axis activity.

2.3.4 Cortisol measures

Analysing samples collected over a specific period of time as a whole instead of referring to key time points allows to comprise information that is contained in repeated measurements otherwise impossible to fathom: 1) whether any changes have occurred over that timeframe and 2) the overall intensity of the change (J. C. Pruessner et al., 2003). This is achieved by computing the Area Under the Curve (AUC) comprises between the Cartesian axis and the values that the variables assumed at the different time points (figure 2.4).

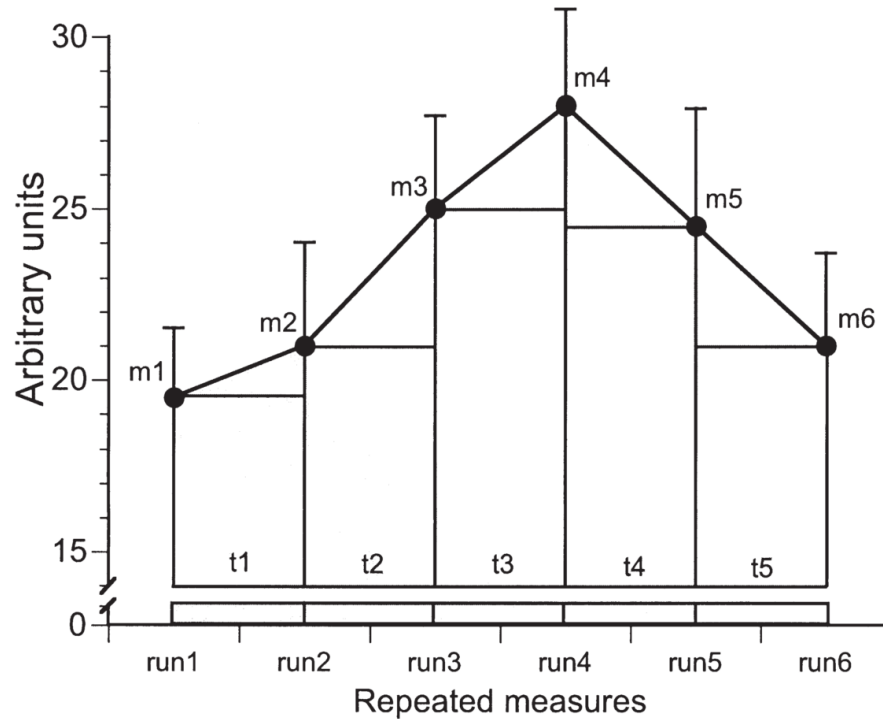


Figure 2.4: The composition of the AUC is illustrated by the triangles and rectangles. M_1 to M_6 denote the single measurements and t_1 to t_6 the interval between the measurement and the overall timeframe (J. C. Pruessner et al., 2003).

I evaluated participants' cortisol basal production across groups (Cortisol levels during the day) using the formula developed by Pruessner et al. (2003) to compute the AUC with the cortisol samples collected at awakening and then at noon and 8 pm. The HPA axis reactivity in individuals exposed and not exposed to abuse was measured quantifying the morning cortisol production in two ways: gauging the overall hormone production and the cortisol variation from the basal line level both measures within the first hour of wake. First the overall production of cortisol in the first hour after awakening (Cortisol Awakening Response to Ground), was calculated as the AUC with the values from the sample collected at awakening, and then at 15, 30 and 60 minutes afterwards, with the same formula used for the Cortisol levels during the day. Finally the variation of the cortisol production within the first hour of wake (Cortisol Awakening Response to Increase) was computed as AUC with respect to increase with cortisol values from the

samples collected at 0, 15, 30 and 60 minutes after awakening controlling for the levels at 0 minutes using the formula proposed by Pruessner et al. (2003).

2.3.5 Statistical analyses

Studies show that differences in HPA axis reactivity after exposure to abuse in childhood can be modulated by gender, as women with a history of abuse in childhood seem to have an increased reactivity, whereas men with a history of abuse in childhood have a decreased reactivity (Heim et al. 2010; De Bellis 2001; Doom et al. 2013). Furthermore, there seems to be different patterns of cortisol reactivity based on gender in individuals at the onset of psychosis, with men patients exhibiting lower cortisol awakening response than women patients (M. Pruessner et al., 2008). For these reasons, I explored the cortisol measures in the entire sample, irrespective of gender, and then in men and women separately.

A two-way ANOVA was used to estimate the effect of the exposure to physical and sexual abuse and psychosis on Cortisol Production During the Day, Cortisol Awakening Response with respect to Ground and Cortisol Awakening Response with respect to Increase respectively. This analysis was first run with the entire sample and then in men and women separately. Physical and sexual abuse in childhood has shown to be linked with an increased probability of exposure to other types of life adversities (e.g. physical or emotional neglect, loss) defining the overall stressfulness of the environment instead of the occurrence of a single negative episode (Suliman et al., 2009). The increase in severity of the level of abuse, from low to severe, can be used to signal the gradual rise in the magnitude of chronic stress to which the participants are exposed, with each level pivotal in the characterisation of the following. To

explore the main effect of abuse was implemented a polynomial contrast to explore which curve best described the variations of the cortisol production with the increase of the abuse severity.

Exposure to overwhelmingly stressful events in childhood has shown to be related with alteration of the range and the pattern of the HPA axis own activity (Sandi & Haller, 2015). Furthermore it is thought that the magnitude of this alteration is connected with the age of the exposure to these experiences, with greater abnormalities related to a younger age (Lupien et al. 2009; Sandi and Haller 2015). Thus to test the relationship between age of abuse and the magnitude of the HPA axis abnormalities I used Pearson correlation to estimate the correlation between each of the three cortisol measure (i.e. the levels of Cortisol levels during the day, Cortisol Awakening Response with respect to Ground and Cortisol Awakening Response with respect to the increase) and the age of abuse. I explored this correlation first in the entire sample and then in men and women separately.

2.4 Interaction between structural MRI and Hypothalamic-Pituitary-Adrenal (HPA) axis function methodology

The brain is rich in glucocorticoid as well as mineralocorticoid receptors and the circadian rhythm of the glucocorticoid hormones influences both the tropism and the functioning of neurons (de Kloet et al., 2005). Additionally a growing body of evidence is linking abnormalities in the HPA axis activities with alteration in brain regions implicated in the neural control of cortisol regulation (e.g anterior cingulate gyrus, orbitofrontal cortex) in the healthy population as well as in individuals with history of trauma in childhood (Lu et al. 2013; Boehringer et al. 2015). It is therefore plausible to consider abnormal levels of cortisol related with atypical brain structures in individuals exposed to environmental stressors. In this section I evaluated whether there is a connection between the HPA axis function and the brain areas showing alterations in individuals reporting abusive experiences. I correlated the cortisol production, as Cortisol levels during the day, Cortisol Awakening Response with respect to Ground and Cortisol Awakening Response with respect to Increase, with the grey matter volume and the cortical thickness of areas showing a significant effect of abuse.

I extracted grey matter volume values and cortical thickness estimations from the brain regions showing significant (i.e. $p < 0.05$ after correction for multiple comparison) differences between individuals exposed and not exposed to abuse. These areas resulted from the two ANCOVA analyses, for grey matter volume and for cortical thickness, as the main effect of abuse as well as the interaction between psychosis and abuse. To maximise the power and the generalizability of these analyses, I used the results from the models that included all participants in the study, which comprise a sample of 81 individuals without abuse exposure (34 controls and 47 cases) and 79 individuals with history of childhood abuse (30 controls and 49 cases). I obtained grey matter volume values using the MarsBar application

(<http://marsbar.sourceforge.net/>) present in the SPM12-2015 toolbox, which allows defining a region of interest and extracting the values of grey matter for those specific regions. I acquired cortical thickness values drawing manually ROIs for the areas significantly affected by the exposure to abuse using the application QDEC in FreeSurfer 5.1.0. The coordinates of the vertex with the maximum value within each cluster was be used as centre of the ROIs. The cortical thickness was obtained using the command-line interface for each ROI. Once I had obtained the data concerning the brain structures I correlated them with the Cortisol levels during the day, Cortisol Awakening Response with respect to Ground and Cortisol Awakening Response with respect to Increase (z-scores) using a Pearson's correlation.

2.5 Candidate personal contribution to the investigation

I joined the GAP and EUGEI study in 2012, and I therefore participated in different phases of the study, such as:

- I. Recruitment: from 2012 to 2014 I have been in charge of recruiting healthy controls with a previous history of exposure to moderate/severe childhood abuse. I screened the study notes of individuals already contacted as part of the bigger study to identify healthy participants with a moderate/severe history of abuse exposure. I then contacted them, presented my study to them and obtained informed consent. I was responsible for their MRI scanning, assessing and collecting saliva samples. From 2012 to 2013 I was in charge of completing the study assessment (MRI scan, clinical assessment and saliva sample collection) for the 1-year follow-up.
- II. Clinical assessment: I actively participated in rating the psychotic symptomatology, using PANSS rating scale in 9 cases.
- III. Cortisol assessment: Saliva tubes were given to patients and controls on the same day of the MRI scans. I was personally involved in explaining the saliva collection procedure and in tracking participants to return their saliva samples, for those I assessed. I was not involved in the laboratory analysis of salivary cortisol, which was done in one of the laboratories at the Institute of Psychiatry, Psychology and Neuroscience. I was responsible for the quality control and

cleaning of the cortisol database. I solely conducted the analyses on the impact of childhood abuse on the cortisol level during the day, cortisol awakening response with respect to the ground and cortisol awakening response with respect to the increase, under the guidance of my PhD supervisors.

- IV. MRI: I was involved in the transport of patients and controls to the MRI suite and attended the MRI sessions for all the 21 participants I assessed. I was solely responsible for the quality controls and pre-processing of the structural images for all the participants in the EUGEI and GAP study. I solely conducted the analyses on the effect of moderate/severe abuse exposure on the brain grey matter volume and cortical thickness, under the supervisor of my PhD supervisors.
- V. I solely conducted the analyses on the integration of the HPA axis activity and neuroimaging findings in relation with the exposure to childhood abuse, under the guidance of my PhD supervisors.

3 Results

Overview of the results

In the section 3.1.1 I will first present the description of the socio-demographic characteristics and the abuse distribution in the entire sample, comparing healthy controls with the patients at their first episode of psychosis. I will then describe the characteristics of the clinical population. As the samples used for the neuroimaging and cortisol analyses are slightly different in composition to the main sample, I will also present the distribution of abuse and the clinical characteristics of individuals included in these two analyses sections (3.1.2 Neuroimaging sample and 3.1.3 Cortisol sample).

In the second part I will then report the results of the neuroimaging (3.2. Results of Structural MRI) and of the cortisol analyses (3.3 Results of Hypothalamic-Pituitary-Adrenal axis activity).

Finally, I will present (3.4 Correlation between brain structure and Hypothalamic-Pituitary-Adrenal axis activity) the evaluation of the potential relationship between the abnormalities shown in the two biological systems in relation to abuse (i.e. brain structure and cortisol).

In each of the sections there will be reported first the results of the analyses in the entire sample and then in each of samples homogenous per gender.

3.1 Socio-demographic characteristics, abuse exposure, and clinical evaluation

3.1.1 Data on the entire sample

3.1.1.1 Socio-demographic data

A total of 191 patients at first episode of psychosis and 156 healthy controls were included in the study. Table 3.1 shows the participant socio-demographic characteristics. There was no significant difference in age between cases and controls while there were significantly more males among patients than among controls. At the time of recruitment cases were more likely to be single, living alone or with parents whereas controls were more often involved in a steady relationship, living with friends or spouse and were more likely to have children. Controls had also a higher level of education (undergraduate or postgraduate) and being of white origin than cases, and were more likely than cases to be in full-time, paid job, and to be either studying or working.

	Cases						Controls						
Age	mean (s.d.) 27.8 (9.1)						mean (s.d.) 29.4 (8.6)						$t_{(345)} = -1.65$ $p = 0.13$
Gender	Male 104 (54.6%)			Female 87 (45.4%)			Male 61 (39.4%)			Female 95 (60.6%)			$\chi^2_{(1)} = 8.17$ $p = 0.004$
Relationship status	Single 131 (60.5%)	Married 22 (11.5%)	Steady relationship 26 (13.5%)	Divorced/ Separated 12 (6.3%)	Widowed 0 (0.0%)		Single 77 (49.4%)	Married 36 (23.1%)	Steady relationship 38 (24.4%)	Divorced/ Separated 2 (1.3%)	Widowed 1 (0.6%)		$\chi^2_{(5)} = 26.82$ $p < 0.001$
Employment Status	Unemployed 116 (60.5%)	Student 20 (10.5%)	Full-time Job 37 (19.5%)		Part-time Job 18 (9.5%)		Unemployed 17 (11.0%)	Student 34 (21.3%)	Full-time Job 75 (48.4%)		Part-time Job 30 (19.4%)		$\chi^2_{(3)} = 89.20$ $p < 0.001$
Education	No qualifications 33 (16.7%)	Compulsory education 46 (24.2%)	Vocational/Tertiary 74 (39.3%)		Higher 38 (19.9%)		No qualifications 2 (1.3%)	Compulsory education 9 (5.8%)	Vocational/Tertiary 54 (34.6%)		Higher 89 (57.3%)		$\chi^2_{(6)} = 87.92$ $p < 0.001$
Living circumstances	Alone 48(24.7%)	Alone with children 12 (6.2%)	Partner 33(18.5%)	Parents/ Family 55(28.3%)	Friends 14(7.2%)	Other 10 (6.4%)	Alone 10 (6.4%)	Alone with children 5 (3.2%)	Partner 16 (10.2%)	Parents/ Family 29(18.4%)	Friends 23(14.6%)	Other 10 (6.4%)	$\chi^2_{(8)} = 33.65$ $p < 0.001$
Ethnic Composition	White Origin 70 (36.2%)	Black Origin 70 (36.2%)	Asian origin 20 (10.6%)	North African 14 (7.4%)	Mixed origin 3 (2.2%)	Other 14 (7.4%)	White Origin 92 (49.2%)	Black Origin 58 (38.1%)	Asian origin 4 (6.5%)	North African 1 (1.6%)	Mixed origin 3 (2.1%)	Other 1 (1.6%)	$\chi^2_{(5)} = 16.7$ $p < 0.023$

Table 3.1: Participants' socio-demographic characteristics (entire sample).

3.1.1.2 Abuse exposure

The CECA interview and the CECA-Q was used to record the exposure to physical and sexual abuse as well as to evaluate the severity of these experiences (Bifulco et al. 1994; Bifulco et al. 2005). According to the authors' criteria, the history of abuse was coded as mild, moderate and severe (Bifulco et al. 1994; Bifulco et al. 2005). Among the individuals who reported abuse exposure in the entire sample, 51.2% experienced both physical and sexual abuse (this percentage was 52.5% among cases and 45.8% among controls). These participants have been included in a severity group according to the most severe experience being it either physical or sexual abuse (e.g. a participant with physical moderate abuse and severe sexual abuse was included in the group severe abuse).

I examined the prevalence of abuse in cases and controls first by comparing individuals without abuse exposure and individuals with any level of abuse, and then investigating the distribution of abuse severity. Patients reported a significantly higher level of exposure to physical or sexual abuse than controls (57.8% of patients were exposed to any level of physical and sexual abuse whereas 49.1% of control reported history of abuse, $\chi^2_{(1)} = 2.78$; $p = 0.05$) (table 3.2). Exploring the severity of abuse (i.e. no abuse exposure, mild, moderate and severe abuse) between groups, cases and controls showed a similar prevalence of moderate abuse (14.1% and 16% respectively) with controls more likely to report episode of mild abuse (17.9% of controls and 7.8% of cases, $\chi^2_{(3)} = 16.58$ $p < 0.001$) and cases to have history of severe physical or sexual violence (30.3% in cases and 14.7% in controls, $\chi^2_{(3)} = 16.58$ $p < 0.001$) (table 3.3).

	Abuse (%)	Not Abuse(%)	
Cases	100 (53.2)	91 (47.8)	$\chi^2_{(1)} = 2.78$ $p = 0.05$
Controls	76 (48.6)	80 (51.4)	

Table 3.2: Exposure to abuse in cases and controls (entire sample).

	Abuse exposure				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	91 (47.8)	15 (7.8)	27 (14.1)	58 (30.3)	$\chi^2_{(3)} = 16.58$ $p < 0.001$
Controls	80 (51.4)	28 (17.9)	25 (16.0)	23 (14.7)	

Table 3.3: Exposure to different levels of abuse severity (entire sample).

Further I investigated the impact of gender on abuse prevalence in the entire sample comparing individuals with and without history of abuse and finally the distribution of the abuse severity. While among male patients there was a significantly higher presence of abuse when compared with male controls (72.5% and 51.8% respectively, $\chi^2_{(1)} = 7.88$ $p < 0.001$) (table 4), there was no difference in abuse prevalence among female participants (58.3% of controls reported history of abuse and 58.4% of cases, $\chi^2_{(1)} = 1.98$ $p = 0.1$) (table 3.5). Looking at the distribution of abuse severity (i.e. no abuse exposure, mild, moderate and severe abuse) it emerges that among females cases were more likely to report severe physical or sexual abuse (32.6 among cases and 9.4% among controls, $\chi^2_{(3)} = 20.09$ $p < 0.001$) (table 3.6) whereas controls showed a higher prevalence of mild abuse level (25% among controls and 9% among cases, $\chi^2_{(3)} = 20.09$ $p < 0.001$). Quite differently in the male sample for each category of abuse there was a bigger proportion of cases than controls, this difference is close to the threshold of significance (table 3.7).

	Abuse(%)	Not Abuse (%)	
Cases	58 (56.9)	44 (13.1)	$\chi^2_{(1)} = 7.88$ $p < 0.001$
Controls	22 (34.9)	41 (65.1)	

Table 3.4: Exposure to abuse in cases and controls (male entire sample).

	Abuse (%)	Not Abuse(%)	
Cases	55 (58.4)	38 (41.6)	$\chi^2_{(1)} = 1.98$ $p = 0.12$
Controls	54 (58.3)	39 (41.7)	

Table 3.5: Exposure to abuse in cases and controls (female entire sample).

	Abuse exposure				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	44 (44.1)	10 (9.8)	15 (14.7)	33 (31.4)	$\chi^2_{(3)} = 6.03$ $p = 0.055$
Controls	41 (63.5)	4 (6.3)	5 (7.9)	13 (22.2)	

Table 3.6: Distribution of abuse in cases and controls (male entire sample).

	Abuse exposure				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	38 (41.6)	8 (9.0)	15 (16.9)	29 (32.6)	$\chi^2_{(3)} = 20.09$ $p < 0.001$
Controls	39 (41.7)	23 (25.0)	22 (24.0)	9 (9.4)	

Table 3.7: Distribution of abuse in cases and controls (female entire sample).

3.1.1.3 Diagnoses and clinical presentation

It was possible to obtain a diagnosis for 191 patients in the sample, and 65.5% of the participants satisfied the criteria for non-affective psychosis and 34.5% for affective psychosis. The most likely diagnosis was schizophrenia or schizophreniform disorder (52.5%), followed by bipolar disorder with psychotic features (13%), psychotic disorder NOS (12%), major depressive disorder with psychotic features (10.5%), schizoaffective disorder (10%) and delusional disorder (1%).

PANSS measurements were successfully collected on a subsample of patients ($n=160$), as for 31 participants it was not possible to obtain enough information to complete the scoring. The average score was 58.25 ± 15.1 . Comparing the mean of the total PANSS score between cases with and without history of abuse I found no significant difference (58.56 ± 13.7 for cases without abuse experience and 60.7 ± 16.5 for cases with history of abuse, $t_{(158)} = -0.56$ $p = 0.53$). Similarly, when comparing the scores for the PANSS subscales positive (14.7 ± 6.2 for cases with abuse experience and 14.2 ± 6.0 for cases without history of abuse, $t_{(158)} = -0.63$ $p = 0.63$), negative (14.5 ± 5.8 for cases with abuse experience and 14.0 ± 5.6 for cases without history of abuse, $t_{(158)} = -0.65$ $p = 0.60$) and general symptoms (29.2 ± 7.7 for cases with abuse experience and 28.3 ± 6.9 for cases without history of abuse, $t_{(158)} = -0.63$ $p = 0.63$) patients with and without history of abuse showed no significant differences. When comparing the total PANSS score and the scores in the different subscales across the groups based on the severity of abuse exposure (i.e. no abuse exposure, mild, moderate and severe abuse), there were no differences across groups in the PANSS subscale negative symptoms ($F_{(3,154)} = 1.9$, $p = 0.12$) (figure 3.1). Patients with history of abuse had higher scores than those without such history in the subscale positive symptoms, this difference was close to the significance threshold ($F_{(3,154)} = 2.5$, $p = 0.06$) and this effect was driven by the moderate

abuse group¹⁰, (figure 3.2). Individuals with abuse showed significantly higher general symptoms than individuals without abuse ($F_{(3,154)} = 3.2$, $p = 0.02$), similarly the moderate abuse group drove this result¹¹. Finally patients with history of abuse had higher general symptoms compared with no abuse group (figure 3.3) and in the total PANSS score ($F_{(3,154)} = 2.7$, $p = 0.04$), again this effect was driven by the moderate abuse group¹², (figure 3.4).

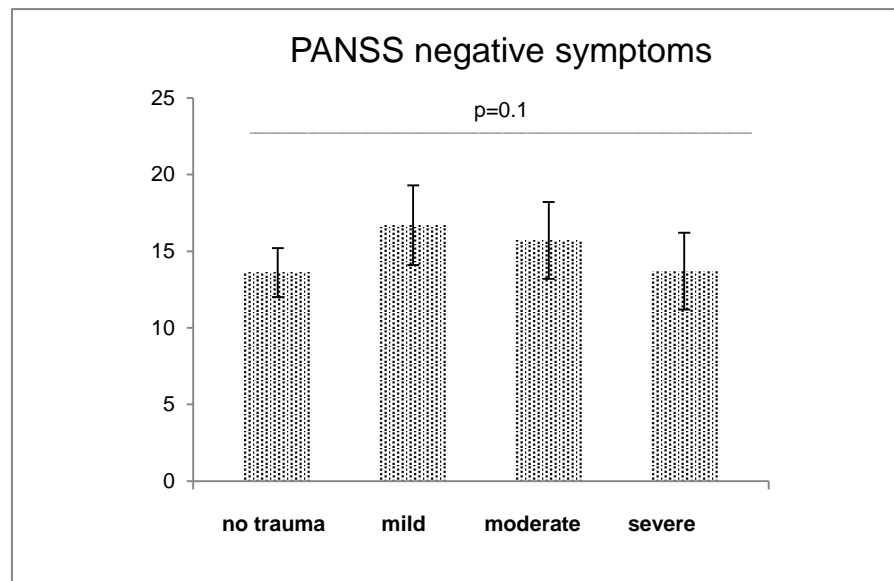


Figure 3.1: PANSS negative symptoms across different abuse severity levels (entire sample); error bars express the standard deviations.

¹⁰ As shown by post-doc analyses with Bonferroni correction (between no abuse and moderate $p = 0.019$; between mild and moderate $p = 0.023$; between moderate and severe $p = 0.031$).

¹¹ As shown by post-doc analyses with Bonferroni correction (between no abuse and moderate $p = 0.017$; between mild and moderate $p = 0.022$; between moderate and severe $p = 0.032$).

¹² As shown by post-doc analyses with Bonferroni correction (between no abuse and moderate $p = 0.019$; between mild and moderate $p = 0.029$; between moderate and severe $p = 0.034$).

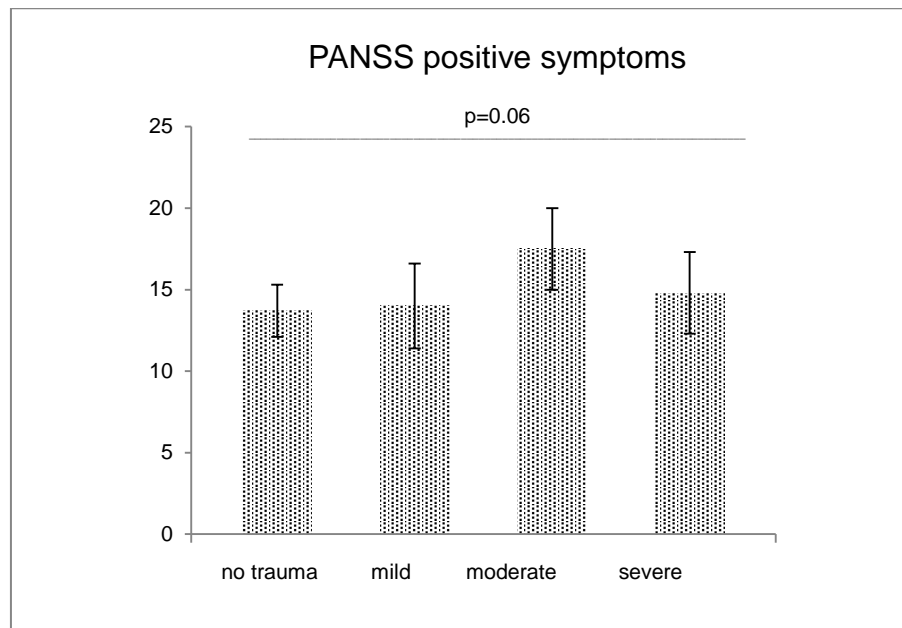


Figure 3.2: PANSS positive symptoms across different abuse severity levels (entire sample); error bars express the standard deviations.

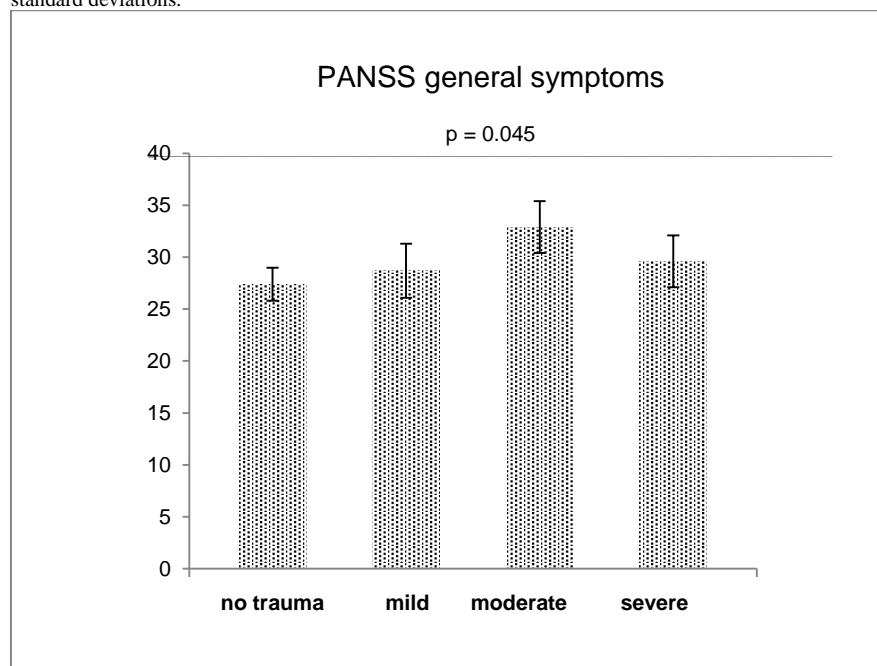


Figure 3.3: PANSS general symptoms across different abuse severity levels (entire sample); error bars express the standard deviations.

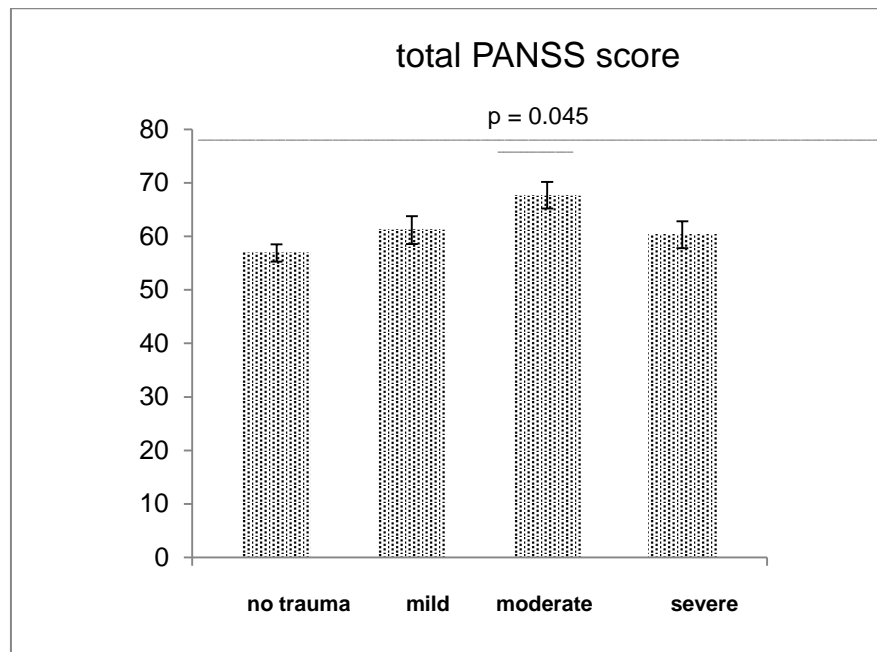


Figure 3.4: total PANSS score across different abuse severity levels (entire sample); error bars express the standard deviations.

I introduced cut-offs to estimate the clinical severity of the participants (mildly ill with a PANSS total score of 58, moderately ill with a PANSS of 75, markedly ill with a PANSS of 95 and severely ill with a greater PANSS total score) (Leucht et al., 2005). Comparing individuals with any levels of abuse and no abuse at all there was no difference across the levels of clinical severity (table 3.8). Similarly there was no significant difference between the levels of patient clinical severity across the different levels of abuse severity exposure (i.e. no abuse exposure, mild, moderate and severe abuse) (table 3.9).

	Clinical severity				
	Mildly ill(%)	Moderately ill(%)	Markedly ill(%)	Severely ill(%)	
Cases with no abuse	42 (57.6)	26 (33.3)	10 (9.1)	0 (0.0)	$\chi^2_{(3)} = 6.34$ $p = 0.055$
Cases with any level of abuse	37 (47.1)	31 (38.6)	12 (10.0)	7 (4.3)	

Table 3.8: Clinical severity between cases with and with abuse exposure (entire sample).

	Clinical severity				
	Mildly ill(%)	Moderately ill(%)	Markedly ill(%)	Severely ill(%)	
Cases with no abuse	42 (57.6)	26 (33.3)	10 (9.1)	0 (0.0)	$\chi^2_{(3)} = 6.03$ $p = 0.055$
Cases with mild abuse	11 (56.3)	6 (25.0)	5 (18.8)	0 (0.0)	
Cases with moderate abuse	11 (34.6)	15 (50.0)	4 (7.7)	4 (7.7)	
Cases with severe abuse	27 (61.0)	15 (31.7)	4 (4.0)	3 (2.4)	

Table 3.9: Clinical severity across different levels of abuse severity (entire sample).

Information about the medication exposure was collected for 181 patients. There was no significant difference in the cumulative dose of antipsychotic, computed as chlorpromazine equivalent, taken by patients exposed and not-exposed to childhood physical or sexual abuse (table 3.10). Likewise, there was

no significant difference in total dose of antipsychotics across the three severity levels of abuse (i.e. no abuse, mild, moderate and severe) (table 3.11).

	Chlorpromazine equivalent		
	Abuse(%)	Not Abuse (%)	
Cases	512.6 (637.2)	182(666.6)	$\chi^2_{(1)}=1.94$ $p = 0.1$

Table 3.10: Chlorpromazine equivalent between cases with and without abuse exposure (entire sample).

	Chlorpromazine equivalent				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	512.6 (637.2)	90.35 (221.2)	188 (447.1)	213 (84.3)	$\chi^2_{(3)}= 2.03$ $p = 0.5$

Table 3.11: Chlorpromazine equivalent between cases with and without abuse exposure (entire sample).

It was possible to collect enough information to estimate the Duration of Untreated Psychosis (DUP) in 146 patients. There was not a statistically significant difference in DUP between cases exposed and not exposed to abuse ($516,5 \pm 2637.3$ days in cases without history of abuse and 182.2 ± 666.6 in cases without history of abuse, $t_{(144)} = -1.35$ $p = 0.11$). Exploring the difference in DUP across the different levels of severity of abuse exposure (i.e. no abuse exposure, mild, moderate and severe abuse), there was no difference in DUP across groups ($F_{(3,146)}= 1.5$, $p = 0.32$).

3.1.2 Neuroimaging sample

A total of 103 patients with first episode psychosis and 65 healthy individuals had an MRI assessment. After the control for the presence of movement artefacts eight scans were excluded (7 cases and 1 control), defining a final sample of 96 cases and 64 controls used for neuroimaging analysis. Similarly to the entire sample, there was no significant difference in age between cases and controls (cases mean age 28.1 ± 7.59 and controls mean age 26.9 ± 8.23 $t_{(166)} = 1.07$; $p = 0.31$) while there were significantly more males among patients than among controls (65.6% of male cases and 54.7% of female controls, $\chi^2_{(1)} = 6.48$; $p = 0.011$).

3.1.2.1 Abuse exposure

Among the individuals who reported abuse exposure in this sub-sample, 53.4% experienced both physical and sexual abuse (this percentage was 54.1 among cases and 47.6% among controls). As explained in the methods section, in the neuroimaging group the abuse exposure has been recoded as a binary variable, distinguishing between individuals with and without a history of physical and sexual abuse. The group of participants reporting abuse comprises individuals with moderate to severe level of abuse only. Individuals with mild abuse were excluded from this analysis. There was no significant difference in abuse distribution between cases and controls in the entire neuroimaging sample (table 3.12). Likewise there was no difference when comparing men and women separately (51.7 % of male controls with abuse and 46.0% of male cases with abuse, $\chi^2_{(1)} = 0.28$; $p = 0.61$; and 42.5 % of female controls with abuse and 58.6% of female cases with abuse, $\chi^2_{(1)} = 2.08$; $p = 0.11$).

	Abuse(%)	Not Abuse (%)	
Cases	49 (51.0)	47 (49.0)	$\chi^2_{(1)} = 3.09$ $p = 0.21$
Controls	30 (46.9)	34 (53.1)	

Table 3.12: Exposure to abuse (any level) in cases and controls (neuroimaging sample).

As explained in the methods, the control group was ‘enriched’ with participants with a history of either moderate or severe levels of abuse. This resulted in an artificial increase in the total number of healthy controls with a history of exposure to physical or sexual abuse included in this sample.

3.1.2.2 Diagnoses and clinical evaluation

A diagnosis was determined for the 96 patients in the sub-sample, 63.7% of the participants satisfied the criteria for non-affective psychosis and 36.3 for affective psychosis. The most likely diagnosis was schizophrenia or schizophreniform disorder (51.5%) followed by bipolar disorder with psychotic features (15.2%), psychotic disorder NOS (12.5%), major depressive disorder with psychotic features (11%), schizoaffective disorder (10.1%) and delusional disorder (0.7%). It was possible to evaluate the PANSS in a total of 69 patients. The average score was 54.5 ± 13.3 . There is no significant difference between cases with and without abuse on PANSS total score (57.1 ± 15.1 for individuals without history of abuse and 60 ± 14.9 for individuals with abuse, $t_{(67)} = -1.01$ $p = 0.3$). Similarly, when comparing the scores for

the PANSS subscales positive (14.5 ± 5.4 for cases with abuse experience and 13.0 ± 5.0 for cases without history of abuse, $t_{(67)} = -1.13$ $p = 0.13$), negative (15.3 ± 6.1 for cases with abuse experience and 14.7 ± 6.1 for cases without history of abuse, $t_{(67)} = -0.93$ $p = 0.62$) and general symptoms (29.5 ± 7.3 for cases with abuse experience and 29.0 ± 7.4 for cases without history of abuse, $t_{(67)} = -0.84$ $p = 0.69$) patients with and without history of abuse showed no significant differences. subscales between cases with and without abuse. Dividing the total PANSS into different levels of clinical severity, ranging from mild to severe (Leucht et al., 2005), there was no difference in clinical severity between patients with any level of abuse exposure and individuals never exposed to abuse (table 3.13).

	Clinical severity				
	Mildly ill(%)	Moderately ill(%)	Markedly ill(%)	Severely ill(%)	
Cases with no abuse	25 (59.6)	10 (23.8)	7 (16.7)	0 (0.0)	$\chi^2_{(3)} = 2.89$ $p = 0.21$
Cases any abuse exposure	22 (48.9)	17 (37.8)	5 (11.1)	1 (2.2)	

Table 3.13: Clinical severity and abuse exposure distribution (neuroimaging sample).

3.1.3 Cortisol sample

A total of 310 participants undertook the cortisol assessment, 8 individuals (6 cases and 2 controls) were excluded as the saliva samples were dry therefore impossible to be analysed. The final sub-sample used for the analysis of cortisol encompassed 169 patients and 133 healthy individuals cortisol. Similarly to the entire sample, there was no significant difference in age between cases and controls (cases mean age 28.1 ± 7.59 and controls mean age 26.9 ± 8.23 $t_{(166)} = 1.07$; $p = 0.51$) while there were significantly more male among patients than among controls (65.6% of male cases and 54.7% of female controls, $\chi^2_{(1)} = 6.48$; $p = 0.011$).

3.1.3.1 Abuse exposure

Among the individuals who reported abuse exposure in this sub-sample, 52.4% experienced both physical and sexual abuse (this percentage was 53.1% among cases and 45.6% among controls). Similarly to the result in the entire sample the number of subjects exposed to any level of abuse during childhood was significantly higher among cases than among controls (table 3.14).

	Abuse (%)	Not Abuse(%)
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Cases	102 (60.4)	67 (39.6)	$\chi^2_{(1)} = 3.51$ $p = 0.03$
Controls	66 (49.6)	67 (50.4)	

Table 3.14: Exposure to abuse (any level) in cases and controls (cortisol sample).

Exploring the distribution of abuse, cases reported a significant higher proportion of severe physical and sexual abuse than controls (table 3.15).

	Abuse exposure				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	67 (39.6)	21 (12.4)	31 (18.3)	50 (29.6)	$\chi^2_{(3)} = 15.84$ $p < 0.001$
Controls	67 (50.4)	29 (21.8)	20 (15)	17 (12.8)	

Table 3.15: Distribution of abuse in cases and controls (cortisol sample).

Investigating the impact of gender on abuse prevalence, there was no significant difference in the proportion of cases and controls exposed and not exposed to any level of abuse, neither in the male (53.2% cases and 49.4% controls respectively exposed to abuse, $\chi^2_{(177)} = 1.84$ $p = 0.6$) nor in female sample (58.2% cases and 49% controls respectively exposed to abuse, $\chi^2_{(107)} = 2.14$ $p = 0.3$). Finally investigating the distribution of the abuse severity, it emerges that female cases are more likely to report severe physical or sexual abuse (34.5 among cases and 11.8% among controls, $\chi^2_{(107)} = 9.07$ $p = 0.02$) (table 3.16) whereas female controls show a higher prevalence of mild abuse level (21.6% among controls and 9.1% among cases, $\chi^2_{(107)} = 9.07$ $p = 0.02$). There was no significant difference across the levels of abuse severity between male cases and controls (table 3.17).

	Abuse exposure				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	26 (51.0)	5 (9.1)	8 (14.5)	19 (34.5)	$\chi^2_{(3)} = 9.07$ p = 0.02
Controls	26 (51.0)	11 (21.6)	8 (15.7)	6 (11.8)	

Table 3.16: Distribution of abuse in cases and controls (female cortisol sample).

	Abuse exposure				
	No Abuse(%)	Mild Abuse(%)	Moderate Abuse(%)	Severe Abuse(%)	
Cases	44 (46.8.0)	12 (12.8)	19 (20.2)	19 (20.2)	$\chi^2_{(3)} = 3.24$ p = 0.3
Controls	41(50.6)	17 (21.0)	12 (14.8)	11 (13.6)	

Table 3.17: Distribution of abuse in cases and controls (male cortisol sample)

3.1.3.2 Diagnoses and clinical evaluation

It was possible to determine the diagnosis for 169 patients in the sample; 67.5% of the participants satisfied the criteria for non-affective psychosis and 32.5% for affective psychosis. The most likely diagnosis was schizophrenia or schizophreniform disorder (53.5%) followed by bipolar disorder with psychotic features (12%), psychotic disorder NOS (12%), major depressive disorder with psychotic features (9%), schizoaffective disorder (11.5%) and delusional disorder (2%).

In a total of 136 patients was collected enough information to complete a PANSS evaluation; the average score was 58.20 ± 15.2 . There was no difference in the total PANSS score between individuals with and

without abuse exposure (56.1 ± 14 for cases with abuse experience and 59.5 ± 15.9 for cases without history of abuse, $t_{(134)} = -0.98$ $p = 0.23$). Similarly, when comparing the scores for the PANSS subscales positive (14.7 ± 6.1 for cases with abuse experience and 14.8 ± 6.2 for cases without history of abuse, $t_{(134)} = -1.13$ $p = 0.31$), negative (13.8 ± 5.6 for cases with abuse experience and 14.9 ± 5.9 for cases without history of abuse, $t_{(134)} = -1.01$ $p = 0.32$) and general symptoms (28.1 ± 6.9 for cases with abuse experience and 29.5 ± 7.7 for cases without history of abuse, $t_{(134)} = -1.26$ $p = 0.35$) I found no statistically significant differences between cases exposed and not-exposed to childhood abuse. Similarly there were no statistically significant differences in the total PANSS score and the scores in the positive, negative and general symptoms across the different levels of abuse distribution (i.e. no abuse, mild, moderate, severe abuse) (total PANSS score = 56.1 ± 14 for cases without abuse – 58.2 ± 14.2 for cases with mild abuse - 63.2 ± 19.2 for cases with moderate abuse - 57.8 ± 14.2 for cases with severe, $t_{(134)} = -1.48$ $p = 0.22$; positive symptoms = 13.7 ± 6.2 for cases without abuse - 14.2 ± 5.5 for cases with mild abuse - 16.3 ± 7.2 for cases with moderate abuse - 14.1 ± 5.8 - 14.1 ± 5.8 for cases with severe abuse, $t_{(134)} = -1.03$ $p = 0.32$; negative symptoms = 13.8 ± 5.6 for cases without abuse - 16.6 ± 6.7 for cases with mild abuse - 15.1 ± 6.2 for cases with moderate abuse - 13.9 ± 5.3 for cases with severe abuse, $t_{(134)} = -1.41$ $p = 0.22$; general symptoms = 28.2 ± 6.9 for cases without abuse - 28.1 ± 7.0 for cases with mild abuse - 30.9 ± 9.2 for cases with moderate abuse - 29.9 ± 6.2 for cases with severe, $t_{(134)} = -0.97$ $p = 0.41$). There was no difference in the patient severity between individuals with any level of abuse when compared with individuals never exposed to abuse (table 3.18). Similarly there were no differences between the different levels of abuse severity and the clinical severity differences (table 3.19).

	Clinical severity			
	Mildly ill(%)	Moderately ill(%)	Markedly ill(%)	Severely ill(%)

Cases with no abuse	30 (55.6)	18 (33.3)	6 (11.1)	0 (0.0)	$\chi^2_{(3)} = 0.89$ $p = 0.8$
Cases with any level of abuse	44 (53.7)	30 (36.6)	7 (8.5)	1 (1.2)	

Table 3.18: Clinical severity and abuse exposure (cortisol sample).

	Clinical severity				
	Mildly ill(%)	Moderately ill(%)	Markedly ill(%)	Severely ill(%)	
Cases with no abuse	30 (55.6)	18 (33.3)	6 (11.1)	0 (0.0)	$\chi^2_{(3)} = 2.92.03$ $p = 0.23$
Cases with mild abuse	11 (61.1)	5 (27.8)	52(11.1)	0 (0.0)	
Cases with moderate abuse	9 (37.5)	12 (50.0)	2 (8.3)	1 (4.2)	
Cases with severe abuse	24 (60.0)	13 (32.5)	3 (7.5)	0 (0.0)	

Table 3.19: Clinical severity across different levels of abuse severity (cortisol sample).

3.2 Results of Structural MRI

I will report the results of the neuroimaging analyses, firstly describing the findings regarding the abnormalities in grey matter volume (VBM analysis) and then the results concerning variations in cortical thickness (FreeSurfer analysis) in cases and controls with and without abuse exposure.

3.2.1 Grey Matter Volume

3.2.1.1 Effect of physical and sexual abuse on grey matter volume in individuals with and without psychosis

Summary: Model 1a (Entire sample)

Differences between individuals with and without abuse exposure

Irrespective of the presence of psychosis, individuals with a history of abuse showed a reduction of grey matter volume in two loci located in the left insula, left medial frontal gyrus, left superior frontal gyrus, right and left anterior cingulate gyrus when compared with individuals without history of childhood abuse. All these areas were significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (table 3.20 and figure 3.5), no clusters passed the more conservative $p < 0.05$ corrected threshold. There were no areas showing greater grey matter volume in individuals with abuse history compared with not-exposed individuals.

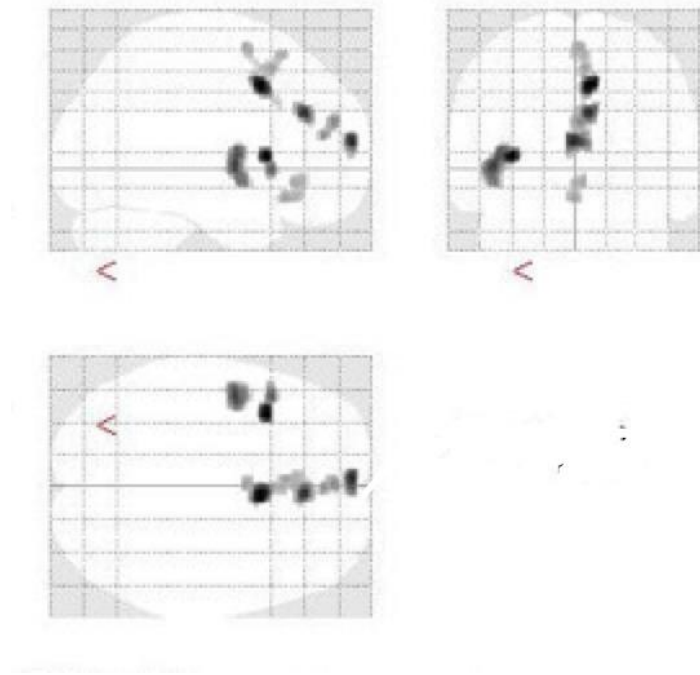


Figure 3.5: Areas significantly smaller between individuals with and without abuse exposure, irrespective of history of psychosis. Glass brain: grey matter volume differences between individuals with and without history of childhood abuse exposure (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels)¹³.

¹³ For each analysis the height threshold was set to $p < 0.001$ uncorrected with a cluster size threshold initially set to 100 voxels. A conservative threshold of $p < 0.05$ cluster corrected FWE was set, followed by a more liberal $p < 0.001$ cluster threshold. If there were clusters which passed the $p < 0.05$ cluster corrected FWE threshold, the analysis was rerun, increasing the cluster size threshold so that only corrected clusters were displayed. This method was applied for each of the following images displaying the effect of abuse exposure on the grey matter volume.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left insula	Brodmann area 13	-34, 14, 4	194	$p < 0.001$
Left medial frontal gyrus	Brodmann area 10	-3, 60, 12	164	$p < 0.001$
Left superior frontal gyrus	Brodmann area 9	0, 50, 22	119	$p < 0.001$
Right anterior cingulate gyrus	Brodmann area 32	4,34,27	162	$p < 0.001$
Left anterior cingulate gyrus	Brodmann area 32	6, 10, 40	375	$p < 0.001$
Right anterior cingulate gyrus	Brodmann area 9	-2, 24, -16	146	$p < 0.001$

Table 3.20: Areas significantly smaller between individuals with and without abuse exposure, irrespective of history of psychosis.

Interaction between psychosis and abuse exposure

There was an interaction between psychosis and abuse. Individuals with psychosis positive for abuse showed a reduction in the grey matter volume of the left precuneus. In contrast, the controls positive for abuse showed a volumetric increase in this area, revealing an interaction between psychosis and history of abuse. This finding was significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.6 and table 3.21), no clusters passed the more conservative $p < 0.05$ corrected threshold.

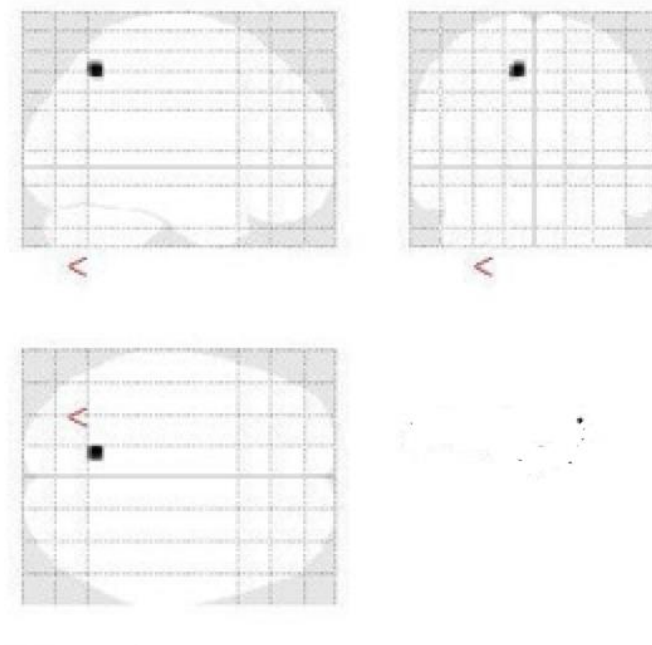


Figure 3.6: Interaction between psychosis and abuse. Area significantly different between individuals with psychosis and abuse exposure and healthy controls with abuse exposure. Glass brain: grey matter difference between cases with abuse exposure and controls with history of childhood abuse, interaction between psychosis and abuse (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left precuneus	Brodmann area 7	-10, 62, 50	163	$p < 0.001$

Table 3.21: Interaction between psychosis and abuse area significantly different between individuals with psychosis and abuse exposure and healthy controls with abuse exposure.

Differences in brain structure between individuals with and without psychosis

When compared with healthy controls, FEP individuals, irrespective of the presence of abuse, show a significant reduction of grey matter volume in the right inferior temporal gyrus and right cerebellum ($p < 0.05$ FWE) and at trend level in the left cerebellum ($p = 0.055$ FWE) (figure 3.7 and table 3.22). There were no areas showing greater grey matter volume in cases compared with controls.

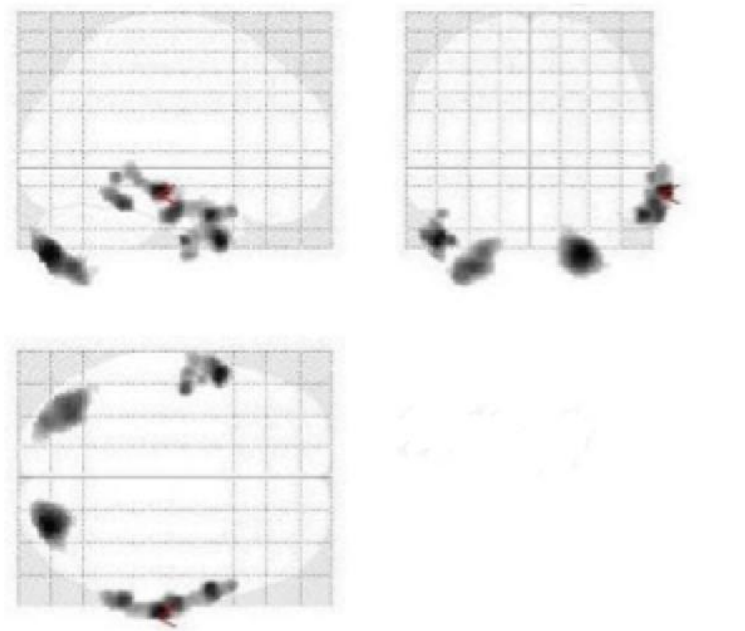


Figure 3.7: Areas significantly smaller between cases and controls, irrespective of abuse exposure. Glass brain: grey matter volume differences between individuals with and without psychosis (height $p < 0.05$ corrected for multiple comparison and cluster size of at least 100 voxels)¹⁴.

¹⁴ In the image 3.7 it was not possible to exclude an area in the left temporal lobe, which was significant at $p < 0.001$ uncorrected but had a similar cluster size of the other areas significant at $p < 0.05$ FWE.

Table 3.22: Areas significantly smaller between cases and controls, irrespective of abuse exposure.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right inferior temporal gyrus	Brodmann area 20	74, -22, 15	1569	$p < 0.001$
Left cerebellum		-32; 74; 52	1375	$p = 0.009$
Right cerebellum		26, 66, 96	1375	$p = 0.055$

3.2.1.2 Patients only: Differences in grey matter volume with and without a history of childhood abuse

Summary Model: 2a (Cases only)

Patients with abuse had a significant reduction of grey matter volume in the right anterior cingulate compared with patients with no history of abuse. This reduction was significant at $p < 0.05$ FWE cluster level (figure 3.8 and table 3.23). There were no areas showing greater grey matter volume in cases with abuse history compared with not-exposed cases.

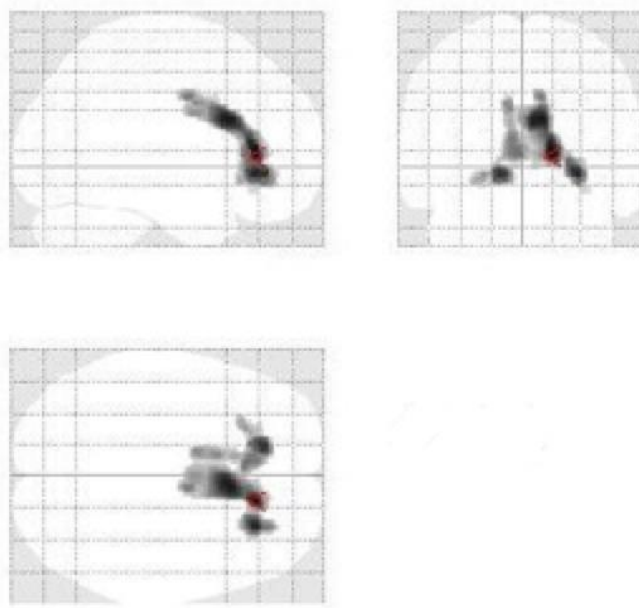


Figure 3.8: Areas smaller in cases with abuse exposure when compared with cases without history of abuse. Glass brain: grey matter volume differences between cases with and without abuse exposure (height $p < 0.05$ corrected for multiple comparison and cluster size of at least 100 voxels).

Table 3.23: Areas significantly smaller in cases with abuse exposure when compared with cases without abuse history.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right anterior cingulate	Brodmann area 32	9, 18, 24 and 18, 32, 6	2143	$p < 0.001$

3.2.1.3 Controls only: Differences in grey matter volume in controls with and without a history of childhood abuse

Summary Model: 3a (Controls only)

Healthy individuals exposed to childhood abuse had increased grey matter volume of the left middle frontal gyrus. This increase was significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.9 and table 3.24), no clusters passed the more conservative $p < 0.05$ corrected threshold. There were no areas showing smaller grey matter volume in controls with abuse history compared with not-exposed controls.

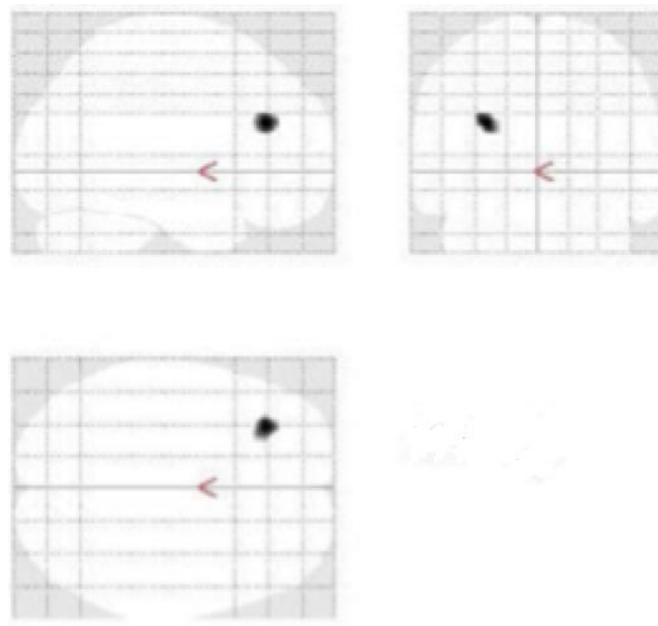


Figure 3.9: Areas significantly bigger in controls with abuse exposure when compared with controls without history of abuse. Glass brain: grey matter difference between healthy controls with and without abuse exposure (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Table 3.24: Areas significantly bigger in controls with abuse exposure when compared with controls without history of abuse.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left middle frontal gyrus	Brodmann area 9	-30; 33; 24	144	$p < 0.001$

3.2.1.4 The role of gender in the effect of physical and sexual abuse on grey matter volume in individuals with and without psychosis

3.2.1.4.1 Gender differences in grey matter volume in patients and controls with and without a history of childhood abuse – *female sample*

Summary: Model 1b (Female only sample)

Differences between individuals with and without abuse exposure

There were no significant result for the effect of abuse on the grey matter volume, irrespective of the presence of psychosis.

Interaction between psychosis and abuse exposure

There were no significant interaction between psychosis and abuse exposure .

Differences between female individuals with and without psychosis

Female individuals with psychosis, irrespective of the history of abuse, showed a reduction in the grey matter volume of the right cerebellum and left cerebellum. These results were significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.10 and table 3.25),

no clusters passed the more conservative $p < 0.05$ corrected threshold. There were no areas showing greater grey matter volume in cases compared with controls.

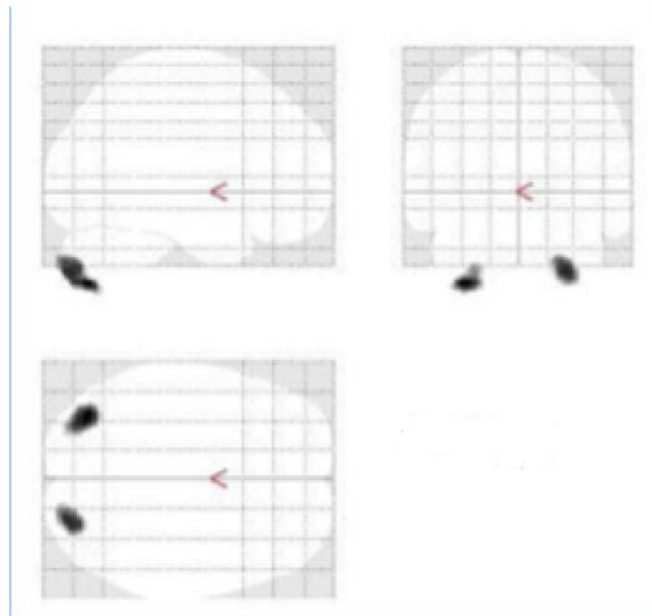


Figure 3.10: Areas significantly smaller in female participants with psychosis compared with female controls, irrespective of history of childhood abuse. Glass brain: grey matter volume differences between individuals with and without psychosis (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left cerebellum		-32; -74; -54	481	$p < 0.001$
Right cerebellum		26; -86; 46	437	$p = 0.001$

Table 3.25: Areas significantly smaller in female participants with psychosis compared with female controls, irrespective of history of childhood abuse.

3.2.1.4.2 Gender differences in grey matter volume in cases with and without a history
of childhood abuse – *female sample*

Summary: Model 2b (Female patients only sample)

There were no significant differences from the comparison between female cases with and without childhood trauma exposure.

3.2.1.4.3 Gender differences in grey matter volume in controls with and without a
history of childhood abuse – *female sample*

Summary: Model 3b (Female controls only sample)

Healthy female controls, exposed to abuse during their childhood showed larger grey matter volume in the left medial frontal gyrus when compared with those not exposed to abuse. This increase was significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.11 and table 3.26), no clusters passed the more conservative $p < 0.05$ corrected threshold. There were no areas showing smaller grey matter volume in controls exposed to abuse in childhood compared with not-exposed controls.

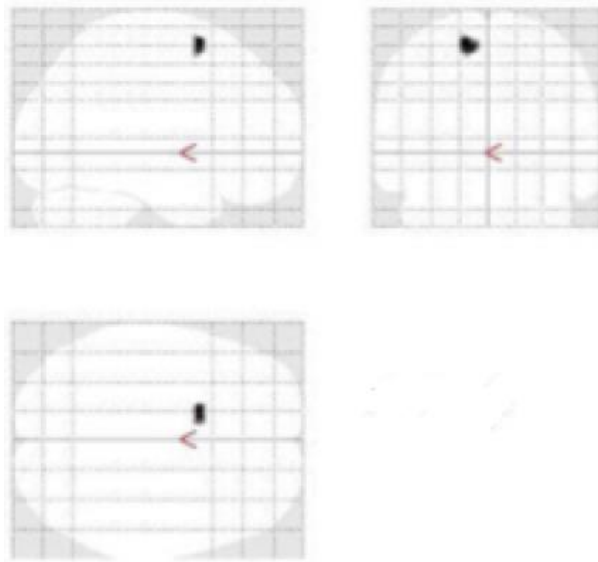


Figure 3.11: Area significantly bigger between controls with and without abuse exposure. Glass brain: grey matter volume differences between individuals with and without abuse exposure (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left medial frontal gyrus	Brodmann area 6	-15; 9; 60	137	$p < 0.001$

Table 3.26: Area significantly bigger between controls with and without abuse exposure.

3.2.1.4.4 Gender differences in grey matter volume in patients and controls with and without a history of childhood abuse – *male sample*

Summary: Model 1c (Male only sample)

Differences between individuals with and without abuse exposure

History of abuse, irrespective of psychosis, was associated with a reduction in the grey matter volume of the right anterior cingulate, left paracentral lobule, left superior frontal gyrus, and left medial frontal gyrus. These results were all significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.12 and table 3.27), no clusters passed the more conservative $p < 0.05$ corrected threshold. There were no areas showing greater grey matter volume in individuals with abuse exposure compared with not-exposed individuals.

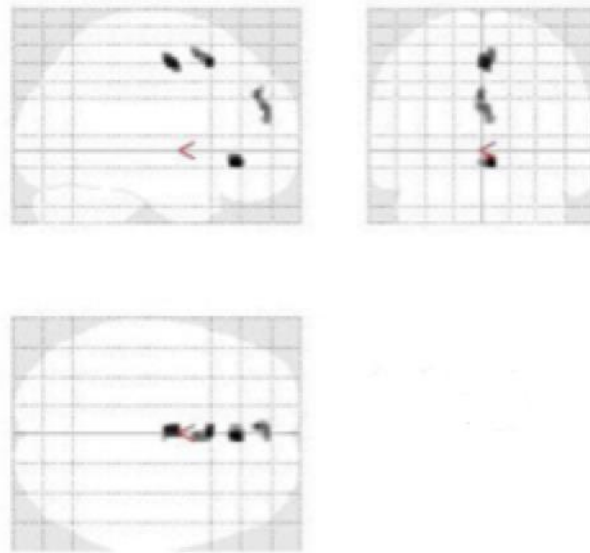


Figure 3.12: Areas significantly smaller between individuals with and without history of childhood abuse, irrespective of the presence of psychosis. Glass brain: grey matter volume differences between individuals with and without abuse exposure in childhood (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Right anterior cingulate	Brodmann area 25	3, 32, -9	162	$p < 0.001$
Left paracentral lobule	Brodmann area 31	-3, 48, 26	100	$p = 0.001$
Left superior frontal gyrus	Brodmann area 6	2, 15, 56	109	$p = 0.001$
Left medial frontal gyrus	Brodmann area 6	0, -6, 48	128	$p < 0.001$

Table 3.27 Areas significantly smaller between individuals with and without history of childhood abuse, irrespective of the presence of psychosis.

Interaction between psychosis and abuse exposure

I found a significant interaction between abuse and psychosis in the left medial frontal gyrus, with cases with abuse showing a reduction in grey matter volume and controls showing an increase. This finding was significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.13 and table 3.28), no clusters passed the more conservative $p < 0.05$ corrected threshold.

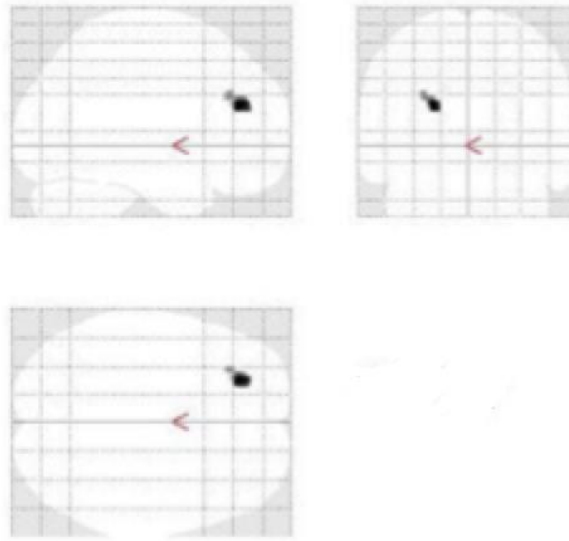


Figure 3.13: interaction between psychosis and abuse; areas significantly different between individuals with psychosis and abuse and healthy controls with abuse exposure. Glass brain: grey matter difference between cases with abuse exposure and controls with history of childhood abuse, interaction between psychosis and abuse (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left medial frontal gyrus	Brodmann area 9	-22; 36; 22	113	$p < 0.001$

Table 3.28: Areas significantly different between individuals with psychosis and abuse exposure and healthy controls with abuse exposure – interaction between psychosis and abuse.

Differences between male individuals with and without psychosis

Male patients, irrespective of the reported abuse, showed a reduction in the grey matter volume in the left middle frontal gyrus when compared with healthy controls. These findings were significant at $p < 0.001$ uncorrected for multiple comparisons and cluster size of at least 100 voxels (figure 3.14 and table 3.29), no clusters passed the more conservative $p < 0.05$ corrected threshold. There were no areas showing greater grey matter volume in cases compared with controls.

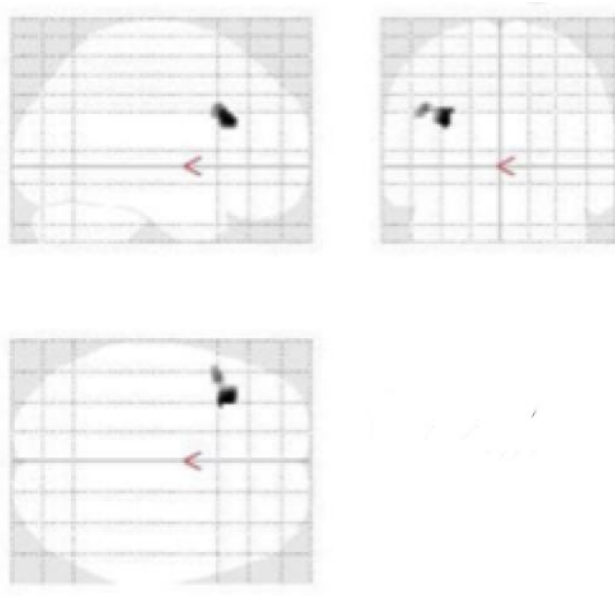


Figure 3.14: Area significantly smaller between cases and controls, irrespective of abuse exposure. Glass brain: grey matter volume differences between individuals with and without psychosis (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Left middle frontal gyrus	Brodmann area 24	-32; 21; 24	185	$p < 0.001$

Table 3.29: Area significantly smaller between cases and controls, irrespective of abuse exposure.

3.2.1.4.5 Gender differences in grey matter volume in cases with and without a history of childhood abuse – male patients

Summary: Model 2c (Male patients only sample)

Male patients with a history of abuse, compared with male patients without a history of abuse, showed a reduction in the grey matter volume of the left inferior frontal gyrus, the left anterior cingulate and right post-central gyrus. These findings were significant at cluster level at $p < 0.05$ FWE (figure 3.15 and table 3.30). There were no areas showing greater grey matter volume in cases with abuse history compared with not-exposed cases.

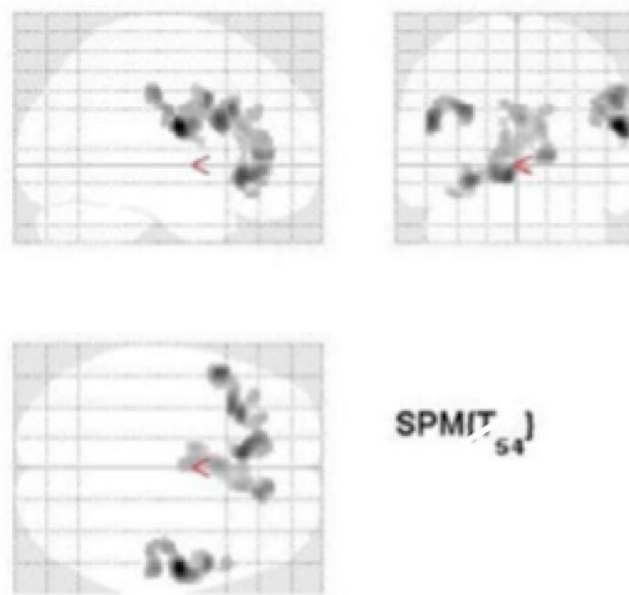


Figure 3.15: Areas significantly smaller in cases with abuse exposure when compared with cases without history of childhood abuse. Glass brain: grey matter difference between cases with and without abuse exposure (height $p < 0.05$ corrected for multiple comparison and cluster size of at least 100 voxels).

Table 3.30: Areas significantly smaller in cases with abuse exposure when compared with cases without history of childhood abuse.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Left inferior frontal gyrus	Brodmann area 9	-56, 12, 22	546	$p < 0.001$
Left anterior cingulate	Brodmann area 24	-6, 26, -8	2218	$p = 0.001$
Right post-central gyrus	Brodmann area 43	56, -9, 18	1174	$p = 0.02$

3.2.1.4.6 Gender differences in grey matter volume in controls with and without a history of childhood abuse – *male sample*

Summary: Model 3c (Male controls only sample)

In healthy individuals, males with a history of abuse showed a reduction in the grey matter volume of the right middle frontal gyrus, right superior temporal gyrus, and right middle temporal gyrus. They also showed larger grey matter volume of the left middle frontal gyrus. These differences were significant at $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels (figure 3.16, 3.17 and table 3.31), no clusters passed the more conservative $p < 0.05$ corrected threshold.

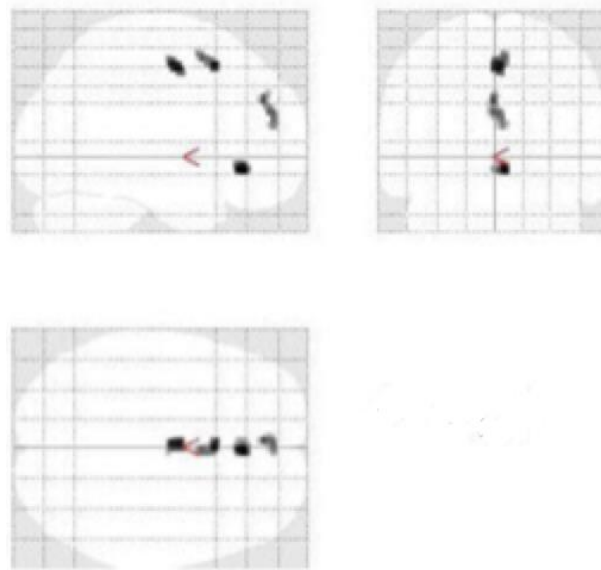


Figure 3.16: Areas significantly smaller in controls with childhood abuse when compared with controls without history of abuse. Glass brain: grey matter difference between cases with and without abuse exposure (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

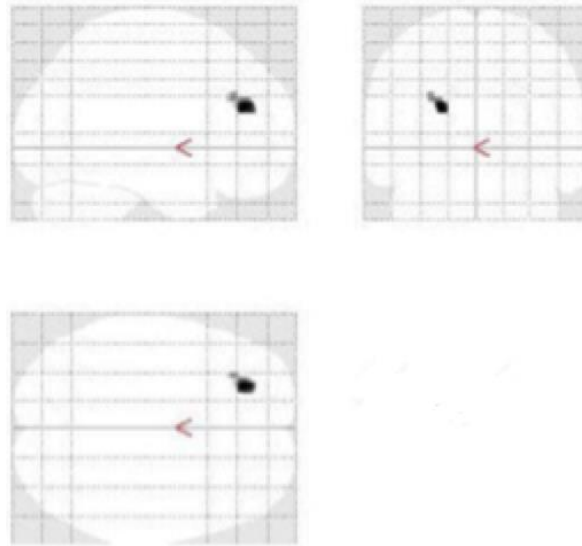


Figure 3.17: Area significantly bigger in controls with exposed to childhood abuse when compared with without abuse exposure. Glass brain: grey matter difference between cases with and without abuse exposure (height $p < 0.001$ uncorrected for multiple comparison and cluster size of at least 100 voxels).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p
Middle frontal gyrus *	Brodmann area 9	39, -63, 27	52	$p < 0.001$
Right superior temporal gyrus *	Brodmann area 22	64, -9, -7	78	$p = 0.001$
Right middle temporal gyrus*	Brodmann area 39	-36, 27, 22	114	$p = 0.001$
Middle frontal gyrus **	Brodmann area 9	-36, 32, 26	158	$p = 0.001$

Table 3.31: Areas significantly different in controls with and without history of childhood abuse (* reduced in controls exposed to abuse when compared with controls never exposed; ** increased in controls exposed to abuse when compared with controls never exposed).

3.2.1.5 Region of interest analysis

Summary: ROIs abuse (Entire sample)

I tested the effect of abuse of the following a-priori defined regions:

- a) Right superior temporal gyrus, inferior orbitofrontal gyrus, medial superior gyrus, superior frontal gyrus, middle temporal gyrus, insula, amygdala and parahippocampal gyrus;
- b) Left inferior frontal gyrus, pre-central gyrus, post-central gyurs, angular gyrus, superior occipital, inferior parietal gyrus and middle occipital gyrus.

There was no grey matter volume differences between individuals exposed and not exposed to childhood abuse in any of the regions of interest selected based on the most recent and comprehensive evidence for grey matter changes in healthy population exposed to abuse (Lim et al., 2014).

Since there are no meta-analyses describing cortical thickness alterations in relation to either exposure to physical and sexual abuse in childhood or for first episode psychosis that can be used to select a-priori areas, I originally decided to investigate whether abnormalities in either cortical surface or cortical thickness were present in the same areas that showed significant differences in the SPM ROI analyses ran in my sample (Section 2.2.5.3.2). The lack of significant differences in these ROIs prevented me from exploring regional difference in surface area and cortical thickness.

3.2.2 Cortical thickness

3.2.2.1 Effect of physical and sexual abuse on cortical thickness in individuals with and without psychosis

Summary: Model 1d (Entire sample)

Differences between individuals with and without abuse exposure

Individuals who reported childhood abuse, irrespective of psychosis, presented a thinning of the cortex in the right medial orbitofrontal gyrus and in the lingual gyrus significant at $p < 0.05$ FWE corrected (figure 3.18 and table 3.32).

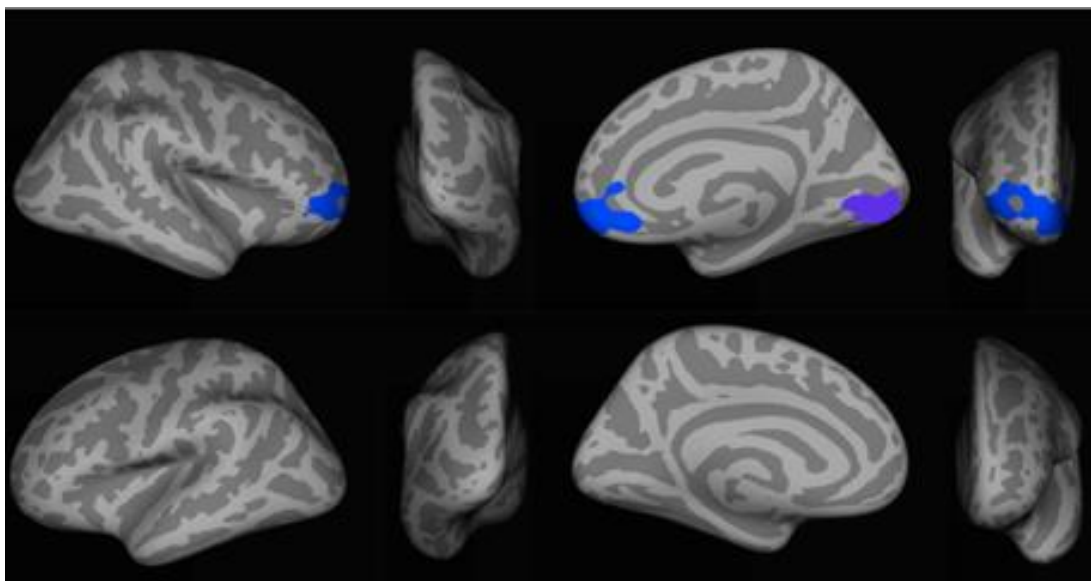


Figure 3.18: Brain regions with significant differences in cortical thickness between individuals with and without childhood history of abuse and controls, irrespective of history of psychosis (blue reduced cortical thickness, red increased cortical thickness).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right hemisphere				
Medial orbitofrontal gyrus	Brodmann area 11	6, 53, 17.7	667.8	p = 0.001
Lingual gyrus	Brodmann area 19	-36, 27, 22	501.07	p = 0.001

Table 3.32: Brain regions with significant differences in cortical thickness between individuals with and without childhood history of abuse and controls, irrespective of history of psychosis.

Interaction between psychosis and abuse exposure

I found an interaction between group (patient/control) and abuse in the right cuneus, right latero orbitofrontal gyrus, right post-central gyrus, right pre-central gyrus, right superior frontal gyrus and right inferior parietal gyrus, all significant at $p < 0.05$ after Montecarlo simulation. This indicated that patients with abuse had a reduction in cortical thickness of these areas while controls with abuse had an increase of these areas (figure 3.19 and table 3.33).

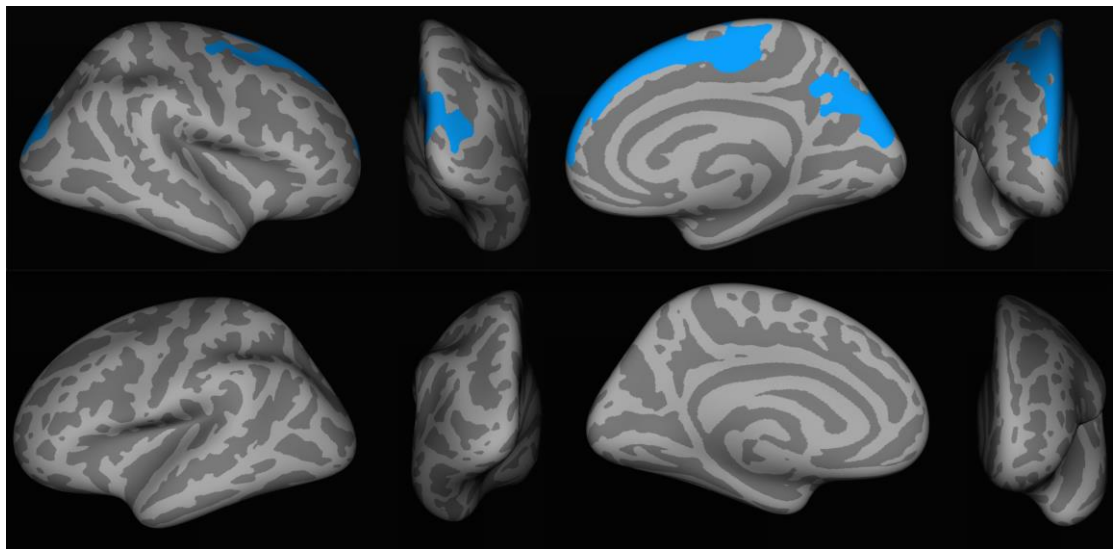


Figure 3.19: Interaction between psychosis and abuse - brain regions with significant differences in cortical thickness between individuals with psychosis and abuse exposure and healthy controls with abuse exposure.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right hemisphere				
Cuneus	Brodmann area 19	7, -80, 28	2843.07	p < 0.001
Latero orbitofrontal gyrus	Brodmann area 13	40, 24, 11	501.07	p < 0.001
Post-central gyrus	Brodmann area 3	33, 33, 42	853.07	p < 0.001
Pre-central gyrus	Brodmann area 4	44, 4, 26	1014.22	p < 0.001
Superior frontal gyrus	Brodmann area 6	15, 10, 55	5262.15	p < 0.001
Inferior parietal gyrus	Brodmann area 39	40, -66, 18	99.07	p < 0.001

Table 3.33: Interaction between psychosis and abuse - brain regions with significant differences in cortical thickness between individuals with psychosis and abuse exposure and healthy controls with abuse exposure – interaction between psychosis and abuse.

Differences between individuals with and without psychosis

Individuals at first episode psychosis, when compared with healthy controls, showed a reduction of cortical thickness in the right supramarginal gyrus and an increase in the right rostral middle frontal gyrus, both significant at trend level ($p = 0.07$ after Montecarlo correction) (figure 3.20 and table 3.34).

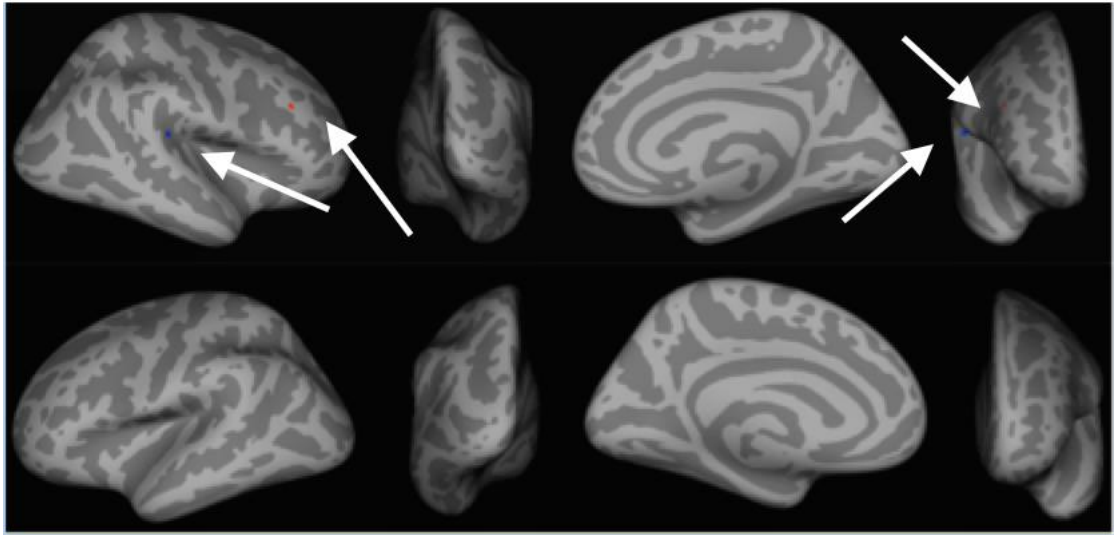


Figure 3.20: Brain regions different at trend level in cortical thickness between, irrespective of abuse exposure (blue reduced cortical thickness, red increased cortical thickness)¹⁵.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right hemisphere				
Rostal middle frontal gyrus**	Brodmann area 19	46, 24, 31	0.14	$p = 0.07$
Supra marginal gyrus*	Brodmann area 40	45, -47, 17	10.83	$p = 0.07$

Table 3.34: Brain regions different at trend level between cases and controls, irrespective of abuse exposure (* reduced cortical thickness, **increased cortical thickness).

¹⁵ Significant cortical areas are overlaid onto inflated cortical surfaces. The inflation provides a better visualisation of the clusters, with darker regions representing sulci.

3.2.2.2 Patients only: Differences in cortical thickness in people with and without a history of childhood abuse

Summary Model: 2d (Cases only)

Patients with first episode of psychosis with a history of abuse, compared with patients with no history of abuse had an increase in cortical thickness in the left pre-central gyrus, and a thinning of the cortex in the right superior frontal gyrus, right medial orbitofrontal gyrus, right inferior parietal gyrus and right cuneus, all significant at $p < 0.05$ FWE corrected (figure 3.21 and table 3.35).

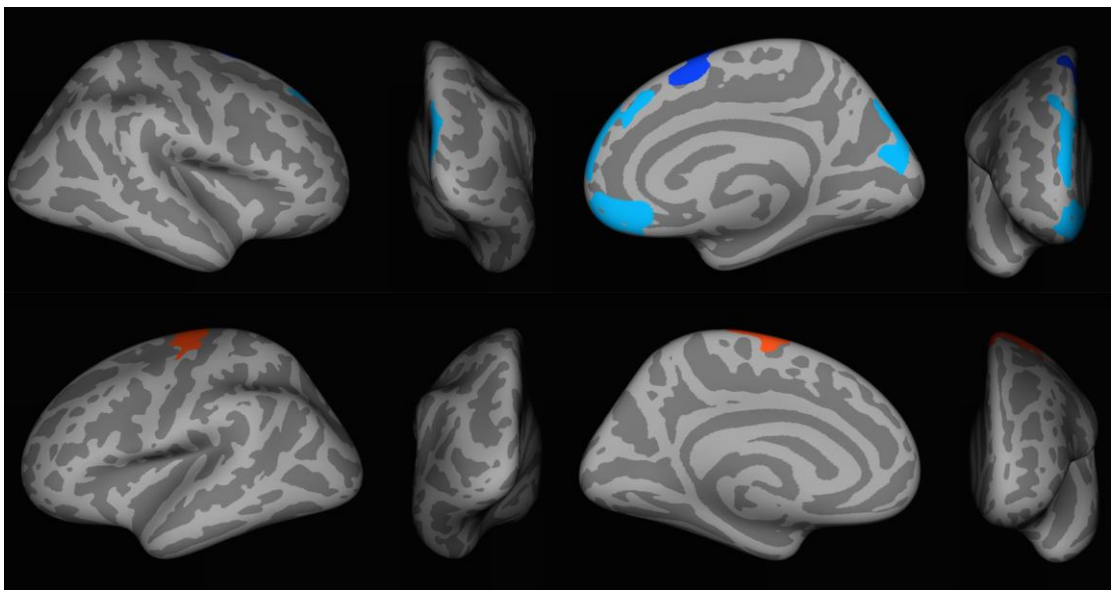


Figure 3.21: Brain regions with significant differences in cortical thickness between cases with and without history of childhood abuse (blue reduced cortical thickness, red increased cortical thickness).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right hemisphere				
Superior frontal gyrus*	Brodmann area 6	8, 52, 29	1052	p < 0.001
Medio orbitofrontal gyrus*	Brodmann area 11	6, 50, 19	1013.35	p < 0.001
Inferior parietal gyrus*	Brodmann area 39	30, 59, 37	753.47	p < 0.001
Cuneus*	Brodmann area 19	5, 76, 21	958.1	p < 0.001
Left Hemisphere				
Pre-central gyrus**	Brodmann area 3	11, 16, 68	555.07	p < 0.001

Table 3.35: Brain regions with significant differences in cortical thickness between cases with and without history of childhood abuse (* reduced cortical thickness, ** increased cortical thickness).

3.2.2.3 Controls only: Differences in cortical thickness in individuals with and without a history of childhood abuse

Summary Model: 3d (Controls only)

There are no significant differences between healthy controls with and without history of childhood abuse.

3.2.2.4 The role of gender in the effect of physical and sexual abuse on grey matter volume in individuals with and without psychosis

3.2.2.4.1 Gender Differences in cortical thickness in patients and controls with and without a history of childhood abuse –*female sample*

Summary: Model 1e (Female only sample)

Differences between individuals with and without abuse

Female participants exposed to childhood abuse, irrespective of history of psychosis, when compared with female not-exposed participants presented an increase in cortical thickness in the right inferior parietal gyrus and right lateral orbitofrontal gyrus significant at $p < 0.05$ after Montecarlo simulation (figure 3.22 and table 3.36).

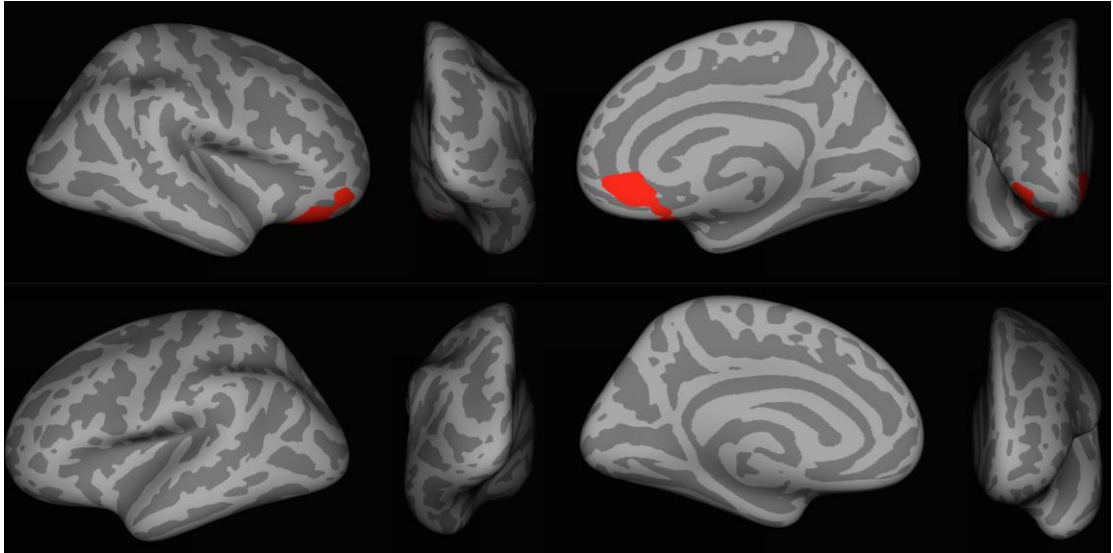


Figure 3.22: Brain regions with significant differences in cortical thickness between individuals with and without abuse exposure, irrespective of psychosis (blue reduced cortical thickness, red increased cortical thickness).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right hemisphere				
Inferior parietal Gyrus **	Brodmann area 7	22, -58, 39	3308.7	$p < 0.001$
Lateral orbitofrontal Gyrus**	Brodmann area 11	22, 28, 10	1371	$p < 0.001$

Table 3.36: Brain regions with significant differences in cortical thickness between individuals with and without abuse exposure, irrespective of psychosis (** increased cortical thickness).

Interaction between psychosis and abuse exposure

An interaction between history of abuse and psychosis was found in the left pericalcarina cortex, right post-central gyrus, right superior frontal gyrus, right superior parietal gyrus, right cuneus and right inferior temporal gyrus, all significant at $p < 0.05$ after Montecarlo simulation. In all the 6 regions, female

patients with first episode psychosis and a history of abuse had a reduction in cortical thickness, while controls with history of abuse had an increase of thickness in these areas (figure 3.23 and table 3.37).

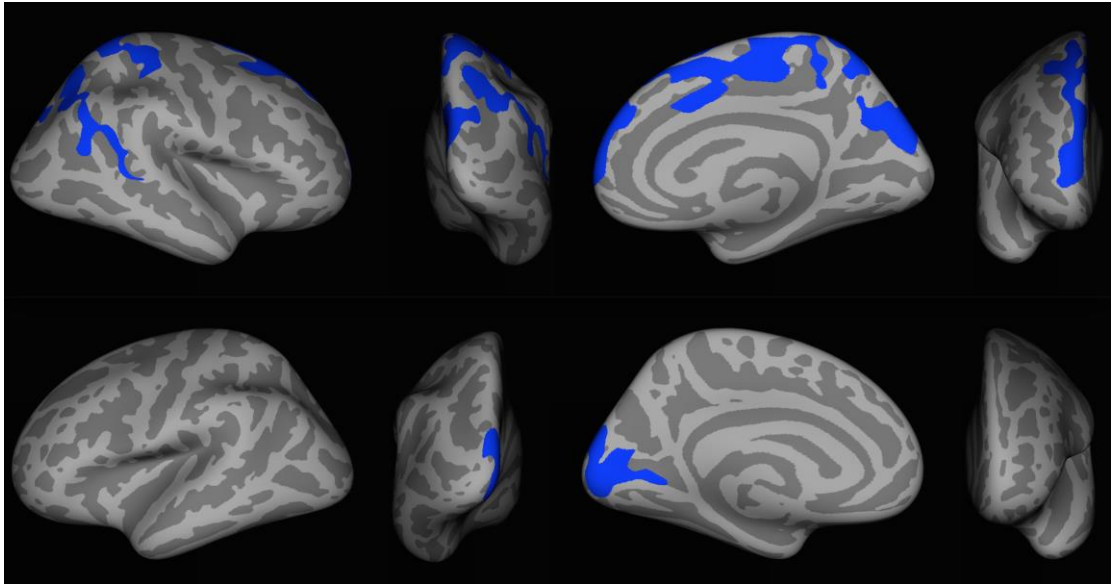


Figure 3.23: Interaction between psychosis and abuse, brain regions with significant differences between individuals with psychosis and abuse exposure and healthy controls with abuse exposure.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Right hemisphere				
Post-central gyrus	Brodmann area 3	31, -30, 60	1671.01	p < 0.001
Superior frontal gyrus	Brodmann area 6	15, 58, 4	1013.3	p < 0.001
Inferior temporal Gyrus	Brodman area 20	56, 50, 11	63077.15	p < 0.001
Superior parietal gyrus	Brodmann area 5	21, 59, 49	1521.22	p < 0.001
Cuneus	Brodmann area 19	5, 70, 35	168.2	p < 0.001
Left Hemisphere				
Pericalcarine gyrus	Brodmann area 44	-11, 78, 15	2308.7	p < 0.001

Table 3.37: Interaction between psychosis and abuse - brain regions with significant differences between individuals with psychosis and abuse exposure and healthy controls with abuse exposure.

Differences between individuals with and without psychosis

Female participants with a history of psychosis, irrespective of abuse exposure, when compared with healthy controls, presented a thinning of the left anterior cingulate cortex significant at trend level (p = 0.06 after Montecarlo correction) (figure 3.24 and table 3.38).

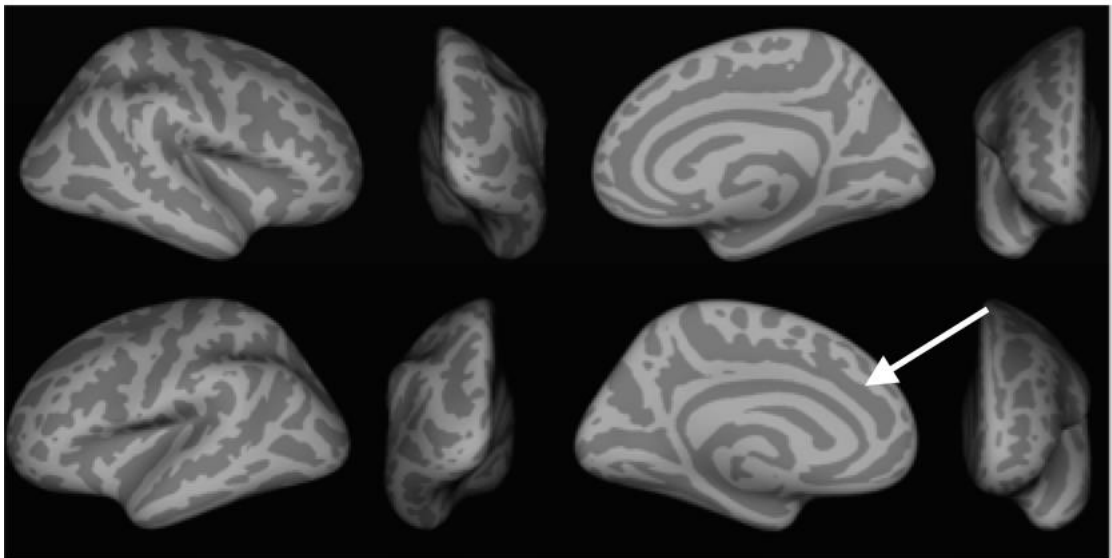


Figure 3.24: Brain regions with significant differences in cortical thickness between individuals with and without history of psychosis (blue reduced cortical thickness, red increased cortical thickness).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Left hemisphere				
Anterior cingulate	Brodmann area 19	4, 44, 28	3.5	p = 0.07

Table 3.38: Brain regions with significant differences in cortical thickness between individuals with and without history of psychosis, irrespective of abuse.

3.2.2.4.2 Gender differences in cortical thickness in cases with and without a history of childhood abuse – *female sample*

Summary: Model 2e (Female patients only sample)

Female individuals with psychosis and abuse exposure presented a thinning of the cortex in the left latero occipital gyrus, significant at $p < 0.05$ FWE corrected when compared with female individuals with psychosis but never exposed to abuse (figure 3.25 and table 3.39).

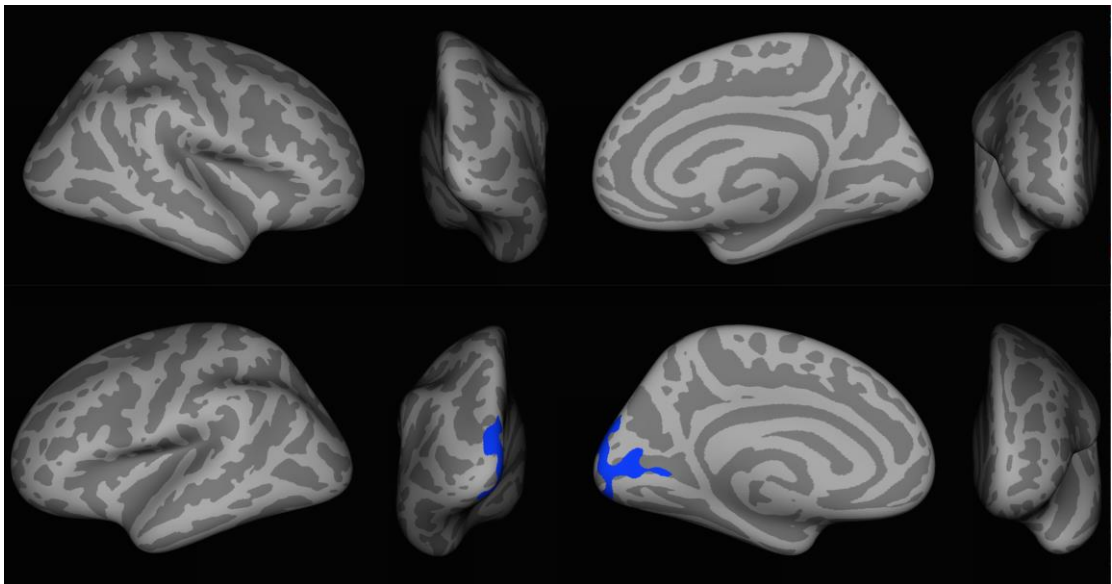


Figure 3.25: Brain regions with significant differences in cortical thickness between cases with and without history of childhood abuse (blue reduced cortical thickness, red increased cortical thickness).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Left hemisphere				
Latero occipital Gyrus	Brodmann area 19	11, 90, 21	385.7	$p < 0.001$

Table 3.39: Brain regions with significant differences in cortical thickness between cases with and without history of childhood abuse.

3.2.2.4.3 Gender differences in cortical thickness in controls with and without a history of childhood abuse – *female sample*

Summary: Model 3e (Female controls only sample)

History of childhood abuse in female controls with history of childhood abuse exposure was associated with an increased cortical thickness in the left lingual gyrus, significant at $p < 0.05$ FWE corrected, (figure 3.26 and table 3.40).

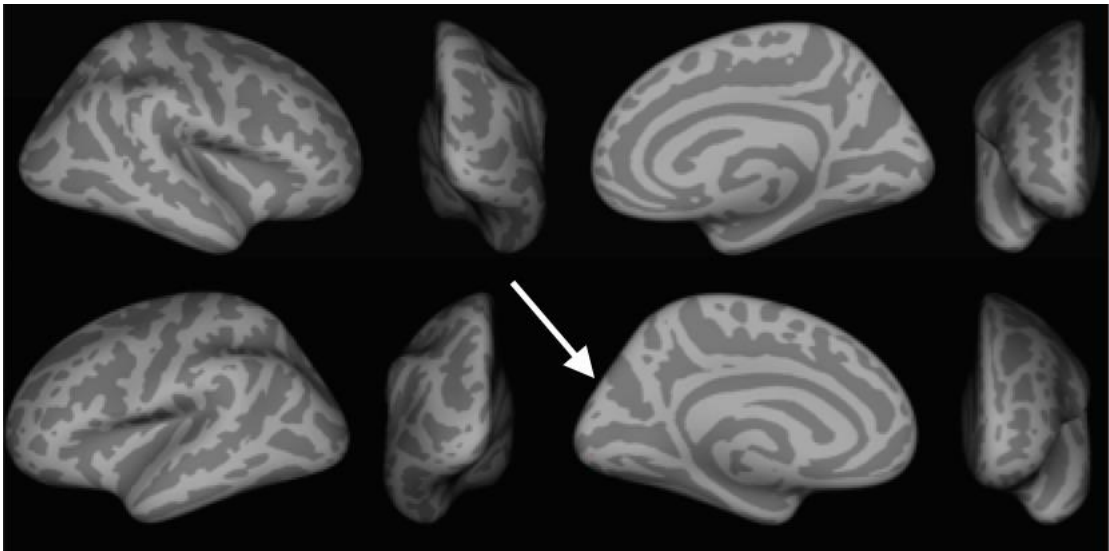


Figure 3.26: Brain regions with significant differences in cortical thickness between controls with and without history of childhood abuse (blue reduced cortical thickness, red increased cortical thickness).

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Left hemisphere				
Lingual Gyrus **	Brodmann area 19	-6, 90, 13	3.7	$p < 0.001$

Table 3.40: Brain regions with significant differences in cortical thickness between controls with and without history of childhood abuse (** increased cortical thickness).

3.2.2.4.4 Gender Differences in cortical thickness in patients and controls with and without a history of childhood abuse – *male sample*

Summary: Model 1f (Male patients only sample)

Differences between individuals with and without abuse

There are no significant differences between male participants with and without abuse exposure, irrespective of their childhood abuse history.

Interaction between psychosis and abuse exposure

There was an interaction between history of abuse and psychosis on the left superior-frontal gyrus. In this area patients at first episode of psychosis who had exposure to childhood abuse showed a reduction in cortical thickness while controls with history of childhood trauma had a thickening of the same area. This was significant at $p < 0.05$ FWE (figure 3.27 and table 3.41).

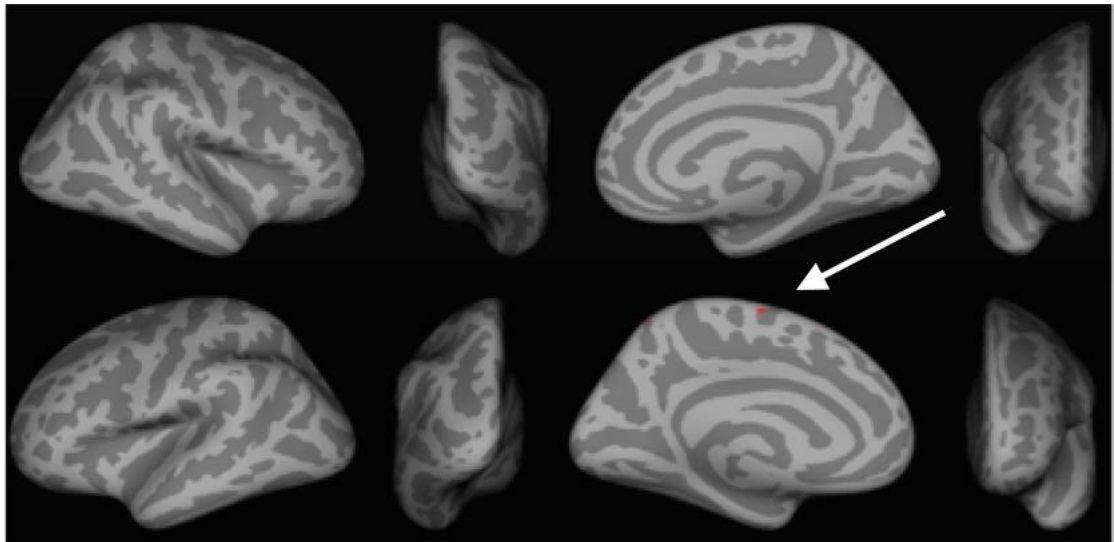


Figure 3.27: Interaction between psychosis and abuse, brain regions with significant differences in cortical thickness between individuals with psychosis and abuse exposure and healthy controls with abuse exposure.

Brain region	Brodmann area	Coordinates	Cluster size	Cluster p FWE
Left hemisphere				
Superior frontal Gyrus	Brodmann area 6	-9, -8, 57	12.2	$p < 0.001$

Table 3.41: Interaction between psychosis and abuse brain regions with significant differences in cortical thickness different between individuals with psychosis and abuse exposure and healthy controls with abuse exposure.

Differences between individuals with and without psychosis

There are no significant differences between male participants with and without psychosis, irrespective of childhood abuse exposure

3.2.2.4.5 Gender differences in cortical thickness in cases with and without a history of childhood abuse – *male sample*

Summary: Model 2f (Male patients only sample)

There was no significant difference in cortical thickness between male cases with and without abuse exposure.

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3.2.2.4.6 Gender differences in cortical thickness in controls with and without a history of childhood abuse – *male sample*

Summary Model 3f (Male controls only sample)

There was no significant difference in cortical thickness between male controls with and without history of abuse exposure.

3.3 Results of Hypothalamic-Pituitary-Adrenal axis activity

In order to evaluate the activity of the HPA axis, I focussed on three different measures of cortisol production, calculated by using the areas under the curve. In particular, I measured the Cortisol Production During the Day, Cortisol Awakening Response with respect to the ground, which measures the cortisol production at awakening as total cortisol concentration within the first hour after awakening, and the Cortisol Awakening Response with respect to the increase, which evaluates the variation in cortisol production from the basal level at awakening within the first hour after awakening. The results for each measure will be presented separately starting with the Cortisol Production During the Day. Each section will show first the effect of physical and sexual abuse on cortisol in individuals with and without psychosis for the entire sample, and then for women and men separately. Finally, I will present the results of the correlations between the different cortisol measures and the age of abuse in the entire sample and in men and women separately.

3.3.1 Cortisol levels during the day

I explored the effect of childhood exposure to physical and sexual abuse on the cortisol levels during the day in individuals with and without psychosis with a two-way ANOVA. The two factors were the presence or absence of psychosis and the different levels of childhood abuse exposure (i.e. no abuse, mild, moderate and severe abuse). As reported in the section 3.1.1.3 there was no difference in the exposure to antipsychotic medication, measured as chlorpromazine equivalent, between cases with and without abuse exposure nor across the different levels of abuse. Therefore I did not use the total amount of chlorpromazine equivalent as covariate in the model. I used this model for the entire sample (169 cases – 59 with no abuse, 27 with mild, 34 with moderate and 49 severe abuse - and 133 controls – 66 with no abuse history, 28 with mild abuse, 21 with moderate abuse and 18 with severe abuse -) and for men (113 cases – 42 with no abuse, 18 with mild, 22 with moderate and 31 with severe abuse - and 80 controls – 39 with no abuse, 17 with mild, 14 moderate and 11 with severe abuse -) and women (56 cases – 18 with no abuse, 10 with mild, 11 with moderate and 17 with severe abuse - and 53 controls – 23 with no abuse, 12 with mild, 9 with moderate and 9 severe abuse) separately.

There was no statistical significant effect of psychosis and abuse in determining the level of cortisol produced during the day in the entire sample ($F_{(7, 302)} = 1.721$, $p = 0.1$) (figure 3.28 and 3.29). The same lack of statistical significance was found in the model with only male ($F_{(7, 193)} = 1.4$, $p = 0.2$) and female ($F_{(7, 109)} = 1.721$, $p = 0.1$) participants.

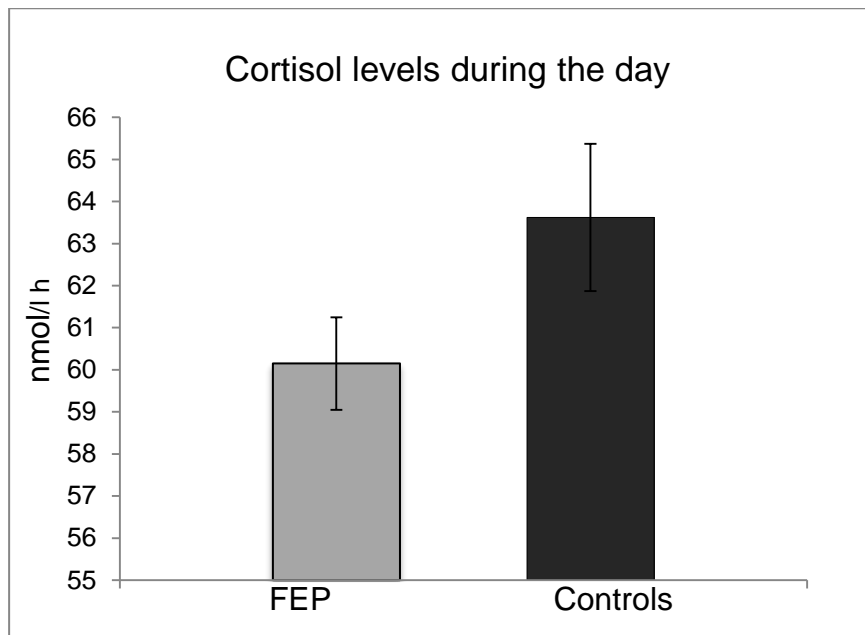


Figure 3.28 Cortisol production during the day; main effect of psychosis (entire sample),); error bars express the standard deviations.

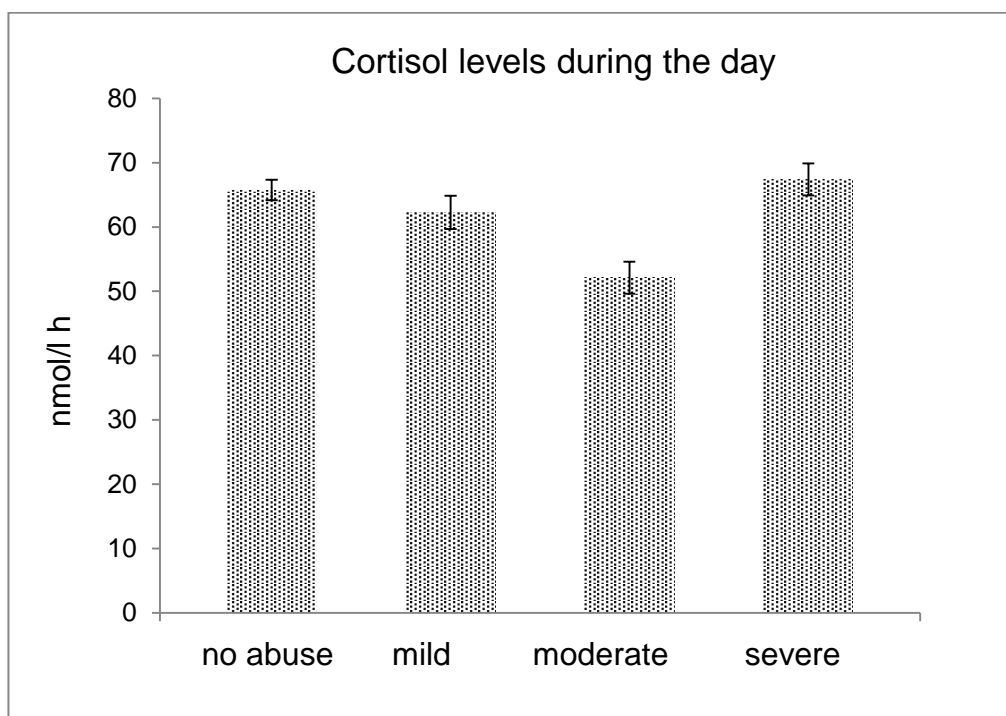


Figure 3.29: Cortisol production during the day; main effect of abuse (entire sample), error bars express the standard deviations..

3.3.2 Cortisol Awakening Response with respect to the ground (CARg)

Similarly to the previous section I used a two-way ANOVA to explore the effect of childhood abuse exposure in individuals with and without psychosis. The two factors were the presence or absence of psychosis and the different levels of childhood abuse exposure (i.e. no abuse, mild, moderate and severe abuse) and I did not include the total amount of chlorpromazine equivalent in the analysis. I used the same model in the entire sample as well as in men and women separately.

Entire sample

This model in the entire sample (169 cases – 59 with no abuse, 27 with mild, 34 with moderate and 49 severe abuse - and 133 controls – 66 with no abuse history, 28 with mild abuse, 21 with moderate abuse and 18 with severe abuse -) sample was statistically significant ($F_{(7,302)} = 5.03$, $p < 0.001$). There was a significant main effect of psychosis on the level of cortisol at awakening ($F_{(1,302)} = 9.35$, $p < 0.01$, $\omega^2 = 0.41$) (figure 3.30) with cases exhibiting an overall lower cortisol awakening response than controls, irrespective of the abuse exposure.

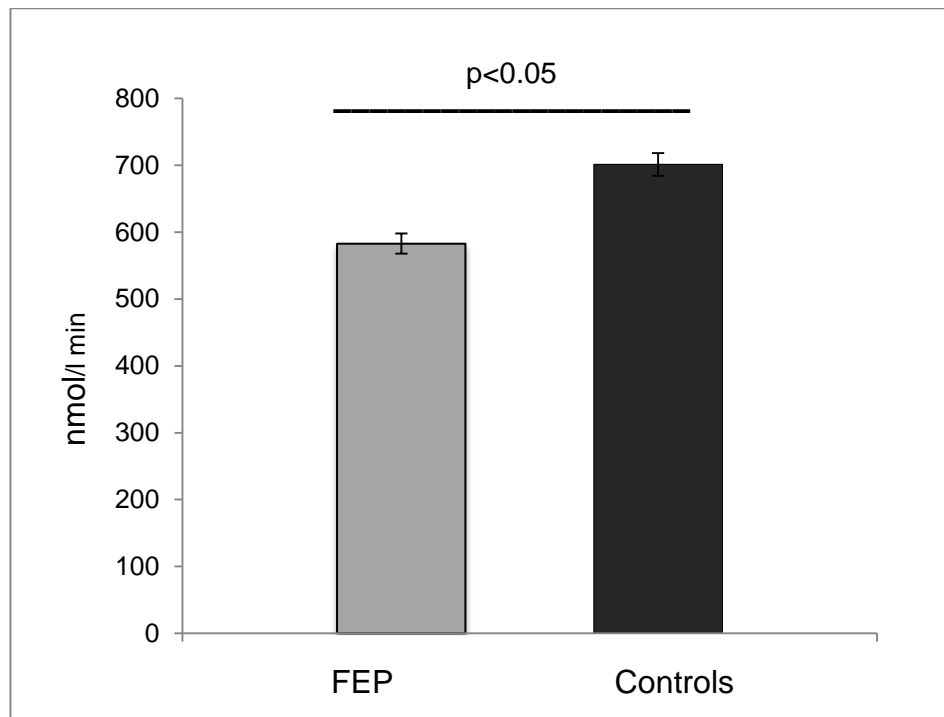


Figure 3.30 Cortisol Awakening Response with respect to the ground; main effect of psychosis (entire sample); error bars express the standard deviations.

There was a difference between CARg in individuals with different levels of abuse exposure that however only reached trend level (main effect of abuse $F_{(3,302)} = 1.55$, $p = 0.097$, $\omega^2 = 0.15$) (figure 3.31).

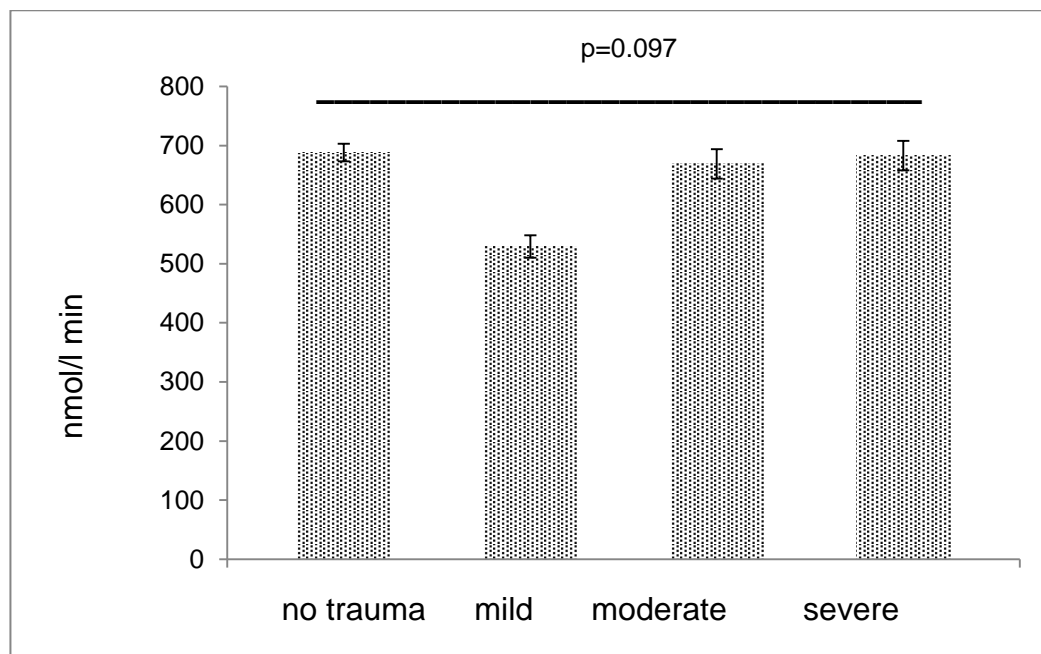


Figure 3.31: Cortisol Awakening Response with respect to the ground; main effect of abuse (entire sample of patients and healthy controls together), error bars express the standard deviations.

Furthermore cases and controls were characterised by significantly different CARg patterns across the different levels of trauma exposure (interaction $F(3,242) = 3.91$, $p < 0.001$, $\omega^2 = 0.45$). Patients showed higher cortisol production at awakening in case of exposure to moderate abuse and a lower in case of severe abuse compared with those without history of trauma, whereas individuals reporting mild or no abuse showed a similar CARg. On the contrary controls with either mild or moderate abuse displayed a blunted CARg compared with those with severe abuse and an higher cortisol production at awakening compared with the CARg present in individuals with no history of childhood abuse (figure 3.32). The observed overall power of the model was 99% explaining the 13% of the variance in the data.

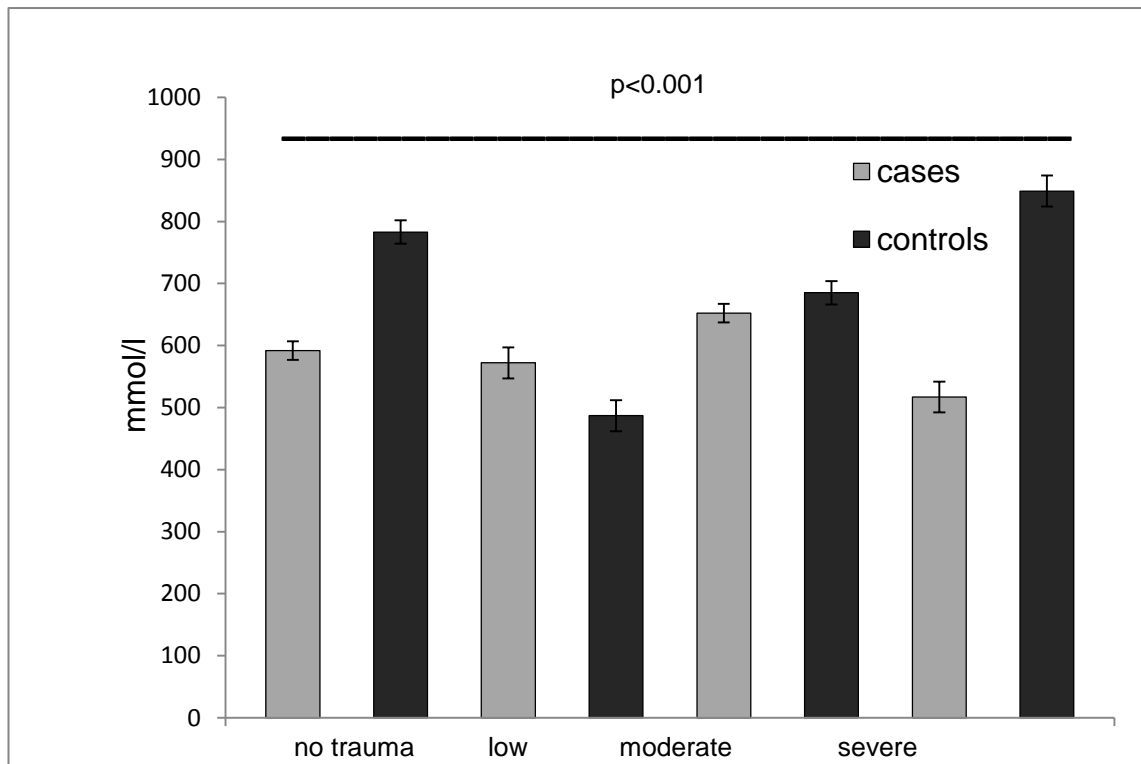


Figure 3.32: Cortisol Awakening Response with respect to the ground; interaction between abuse and psychosis (entire sample); error bars express the standard deviations.

Male sample

The model investigating exposure to childhood abuse and presence of psychosis to explain the variation of CARg among male participants (113 cases – 42 with no abuse, 18 with mild, 22 with moderate and 31 with severe abuse - and 80 controls – 39 with no abuse, 16 with mild, 14 moderate and 11 with severe abuse -), showed an overall significant effect ($F_{(7,193)} = 4.10$, $p = 0.023$). Cases showed lower CARg levels than controls (main effect of psychosis ($F_{(1,193)} = 4.75$, $p < 0.001$, $\omega^2 = 0.20$) (figure 3.33).

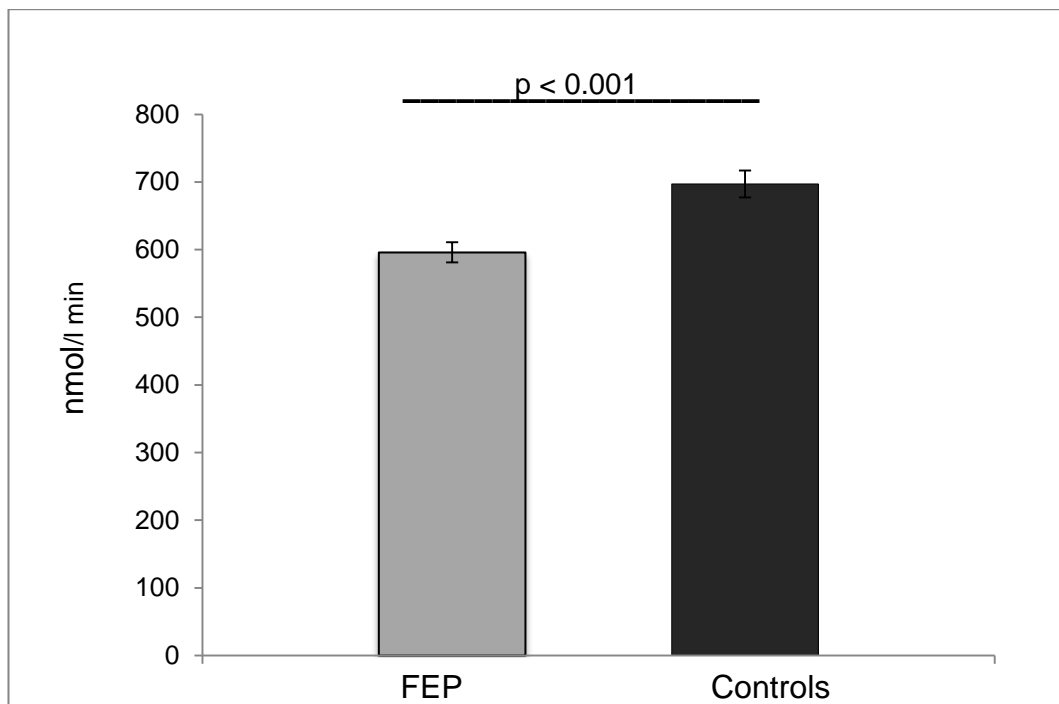


Figure 3.33; Cortisol Awakening Response with respect to the ground; main effect of psychosis (male sample); error bars express the standard deviations.

There were significant differences in CARg between participants exposed and not exposed to childhood abuse, (main effect of abuse ($F_{(3,193)} = 4.12$, $p < 0.05$, $\omega^2 = 0.03$). The best fit for the data from the planned comparison emerged to be a cubic trend ($p < 0.001$). There is in fact a blunted CARg for mild abuse

compared with the higher CARg displayed by individuals with no history of childhood abuse, and higher for moderate abuse and again a blunted CARg for severe abuse (figure 3.34).

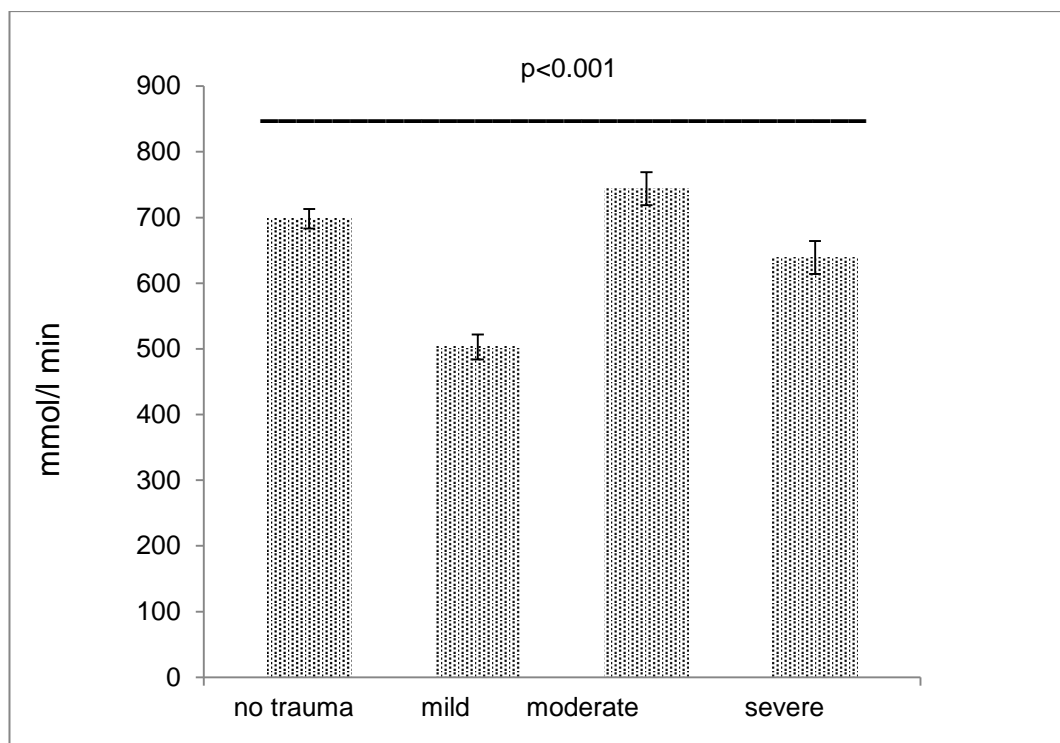


Figure 3.34 Cortisol Awakening Response with respect to the ground; main effect of abuse (male sample of patients and healthy controls together); error bars express the standard deviations.

Male patients exhibited higher CARg in case of exposure to moderate abuse and a lower in presence of severe abuse with level close to baseline (cases with no history of abuse) when mild abuse was reported; this pattern was significantly different from what showed by healthy controls signifying the presence of an interaction between abuse and psychosis (interaction $F_{(3,193)} = 2.30$, $p = 0.021$, $\omega^2=0.76$) (figure 3.35). Indeed among controls all the levels of exposure to childhood abuse were associated with a smaller CARg compared with the values exhibited by individuals with no history of abuse; this difference was more marked for participants exposed to mild abuse nonetheless was present in the ones reporting moderate as well as severe abuse. The model explained 18% of the variance and its power was 98%.

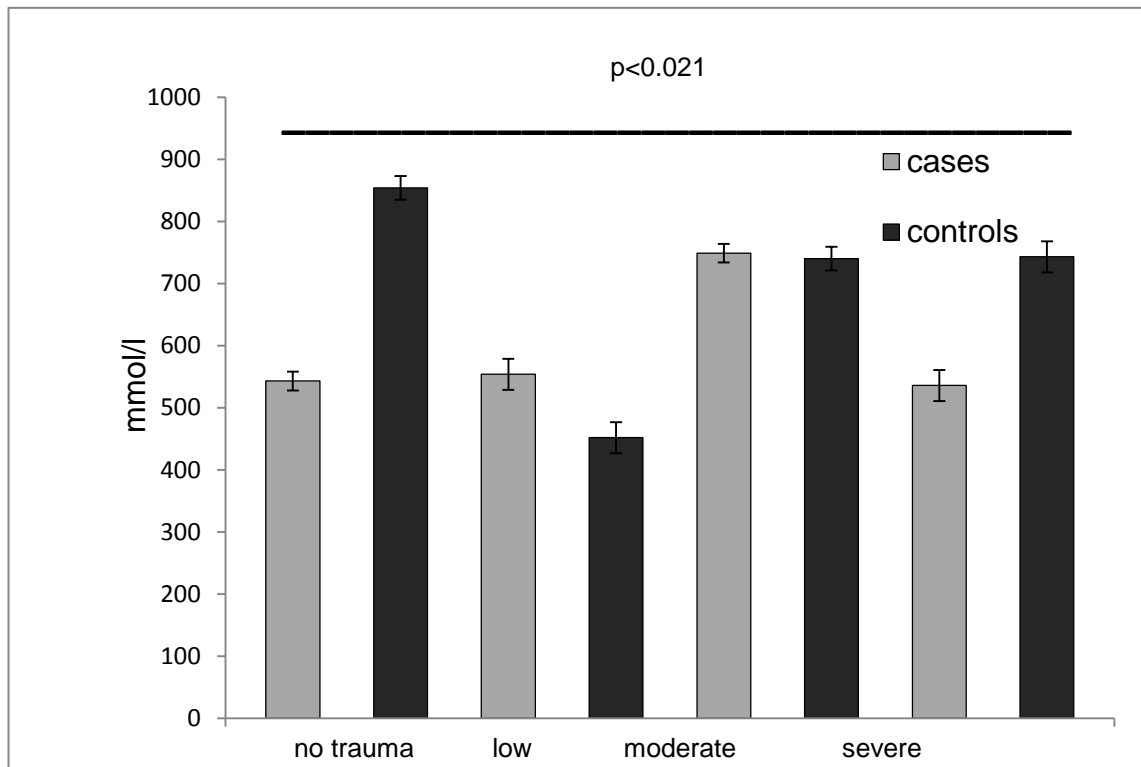


Figure 3.35 Cortisol Awakening Response with respect to the ground; interaction between abuse and psychosis (male sample); error bars express the standard deviations.

Female sample

The model with female participants only (56 cases – 18 with no abuse, 10 with mild, 11 with moderate and 17 with severe abuse - and 53 controls – 23 with no abuse, 12 with mild, 9 with moderate and 9 severe abuse -) was able to significantly explain the variation in CARg using the effect of psychosis and abuse exposure ($F_{(7,109)} = 2.20$, $p = 0.046$). There was a significant main effect of psychosis ($F_{(1,109)} = 3.77$, $p = 0.022$, $\omega^2=0.38$), with female patients showing a consistently blunted CARg when compared with female healthy controls, irrespective of trauma exposure (figure 3.36).

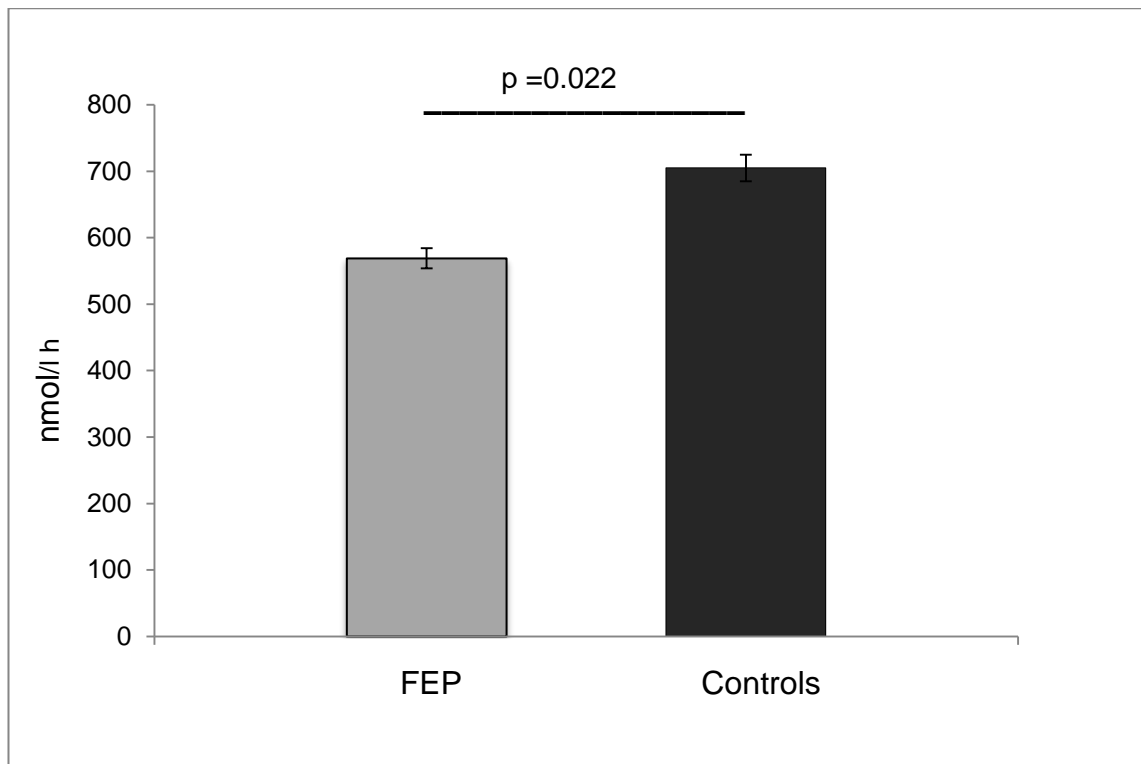


Figure 3.36 Cortisol Awakening Response with respect to the ground; main effect of psychosis (female sample) error bars express the standard deviations.

There was no main effect of abuse on the CARg levels ($F_{(3,109)} = 1.4$ $p = 0.2$)

Furthermore, there was a significant interaction between abuse and psychosis ($F_{(3,109)} = 2.80$, $p = 0.045$, $\omega^2=0.47$), with female patients showing a progressive lower CARg as the severity of trauma experience increased, and female controls displaying higher CARg in case of severe abuse and lower CARg for mild and moderate abuse compared to the CARg of controls without abuse exposure (figure 3.37).

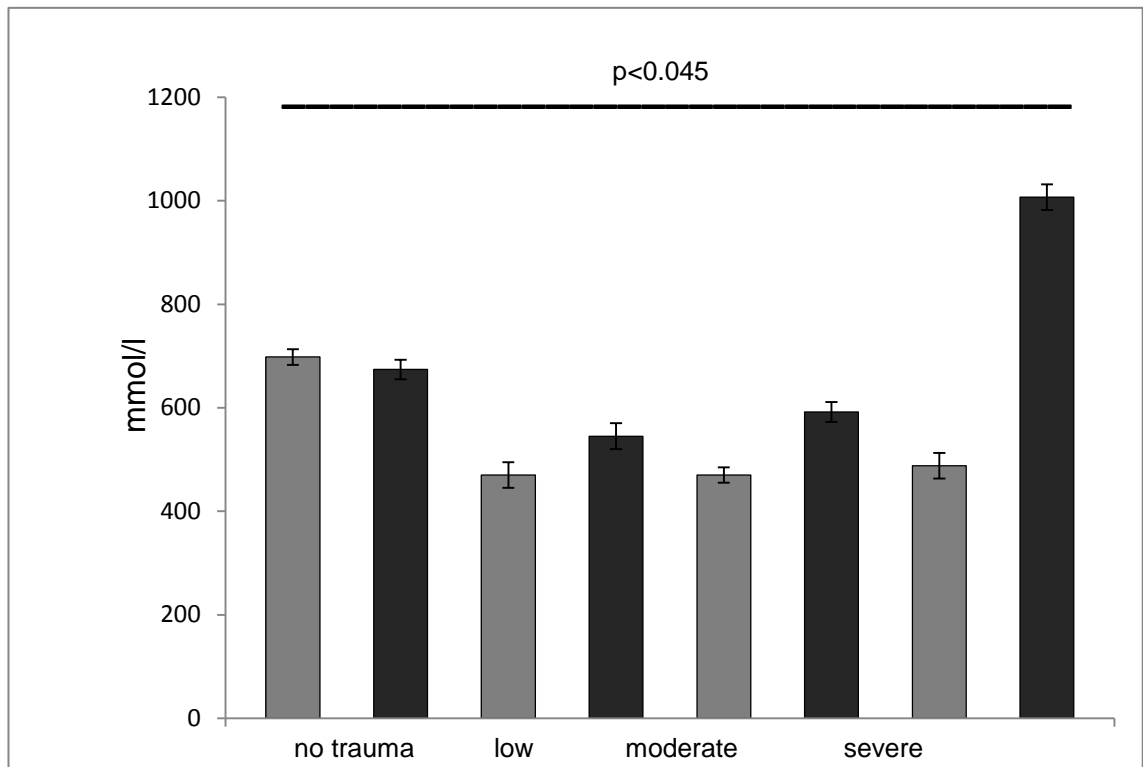


Figure 3.37 Cortisol Awakening Response to ground; interaction between abuse and psychosis (female sample); error bars express the standard deviations.

3.3.3 Cortisol Awakening Response with respect to the increase (CARi)

The model including psychosis and abuse to explain the variation in the CARi in the entire sample (169 cases – 59 with no abuse, 27 with mild, 34 with moderate and 49 severe abuse - and 133 controls – 66 with no abuse history, 28 with mild abuse, 21 with moderate abuse and 18 with severe abuse -) was not statistically significant ($F_{(3,302)} = 1.11$, $p = 0.4$). The same lack of statistical significance was found in the model with only male participants (169 cases – 59 with no abuse, 27 with mild, 34 with moderate and 49 severe abuse - and 133 controls – 66 with no abuse history, 28 with mild abuse, 21 with moderate abuse and 18 with severe abuse -) ($F_{(3,193)} = 1.3$, $p = 0.2$). The model with female participants (169 cases – 59 with no abuse, 27 with mild, 34 with moderate and 49 severe abuse - and 133 controls – 66 with no abuse history, 28 with mild abuse, 21 with moderate abuse and 18 with severe abuse -) was statistically significant ($F_{(3,109)} = 2.60$, $p = 0.02$) with a main effect of abuse ($F_{(3,109)} = 5.50$, $p < 0.001$, $\omega^2=0.88$). Cases and controls exhibited the same pattern in response to the incremental severity of abuse exposure with blunted in cortisol production for mild and moderate level of abuse and higher for severe abuse. The planned analyses showed a quadratic trend in the CARi pattern with a blunted CARi for mild abuse and a higher for moderate and severe ($p<0.001$) (figure 3.38).

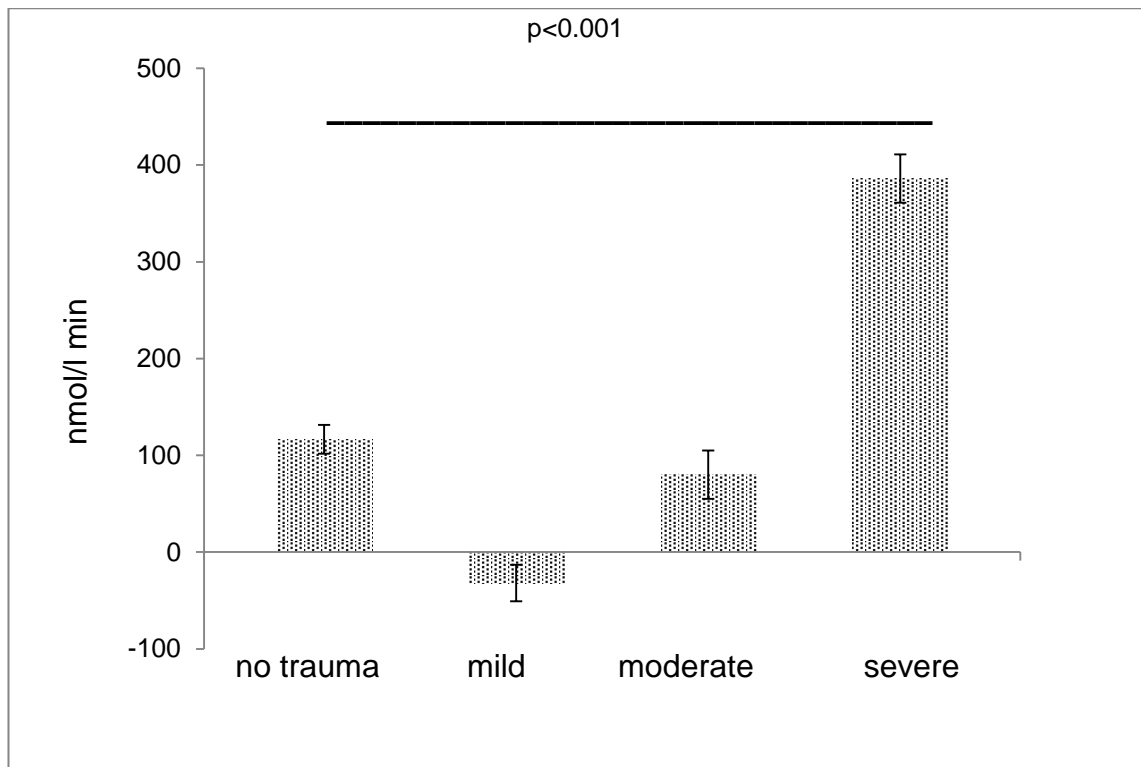


Figure 3.38; Cortisol Awakening Response to Increase; main effect of abuse (female sample) error bars express the standard deviations.

3.3.4 Correlation between the different cortisol production measures and the age of abuse

There was no statistical significant correlation between Cortisol Production During the day, Cortisol Awakening Response with respect to the ground and Cortisol Awakening Response with respect to the increase and age at time of the abuse in the entire sample or in cases and controls separately, and when considering male gender. In contrast, female cases showed a positive correlation between the age at time of the abuse and the Cortisol Awakening Response with respect to the ground ($r=0.50$, $p = 0.032$). None of the other correlations was statistically significant.

3.4 Correlation between brain structure and Hypothalamic-Pituitary-Adrenal axis activity

In this section I report the findings of the correlation between the cortical thickness and the HPA axis activity in areas significantly (i.e. $p < 0.05$ FWE) different between individuals with and without history of childhood abuse. These areas were chosen from the results of the GLM investigating the entire sample (section 3.2.2.1). In addition, I also examined correlations between cortical thickness and HPA axis activity where there was a significant interaction (i.e. $p < 0.05$ FWE) between abuse and the presence of psychosis from the above-mentioned GLM model (section 3.2.2.1). The Cortisol levels during the day, Cortisol Awakening Response with respect to the ground (CARg) and Cortisol Awakening Response with respect to the increase (CARi) were used to investigate HPA axis function. Furthermore, I investigated the relationship between cortisol and regions where there was a significant difference in cortical thickness (i.e. $p < 0.05$ FWE) between cases with and without a history of childhood abuse (section 3.2.2.3). Previous sub-analyses (section 3.2.2.4) examined cortical thickness in each gender separately, however these were conducted in smaller samples, and so the results of those sub-analyses were not included in the current analysis.

3.4.1. Cortical thickness and Hypothalamic-Pituitary-Adrenal axis activity in regions showing a main effect of abuse

There were 2 regions from the cortical thickness analysis in the entire sample (section 3.2.2.1) that survived the $p < 0.05$ FWE threshold. Both right medial orbitofrontal cortex and right lingual gyrus were negatively correlated with the cortisol levels during the day ($r = -0.30$; $p = 0.003$ and $r = -0.24$; $p = 0.02$, respectively) (table 3,41). There was no significant correlation between Cortisol Awakening Response to

ground (CARg) and those areas. The Cortisol Awakening Response with respect to the increase showed a negative significant correlation with both right medial orbitofrontal cortex and right lingual gyrus ($r = -0.25$; $p = 0.02$ and $r = -0.25$; $p = 0.02$ respectively)(table 3.42)¹⁶.

Brain region	Cortisol level during the day	CARg	CARi
Right hemisphere			
Lingual gyrus	$r = -0.30$; $p = 0.003$	$r = -0.75$; $p = 0.4$	$r = -0.25$; $p = 0.02$
Medial orbitofrontal gyrus	$r = -0.24$; $p = 0.02$	$r = -0.41$; $p < 0.7$	$r = 0.24$; $p = 0.03$

Table 3.42: Correlation between HPA axis activity and cortical thickness in areas significantly different in individuals with and without abuse exposure

3.4.2. Cortical thickness and Hypothalamic-Pituitary-Adrenal axis activity in areas showing effect between presence of psychosis and abuse

There were 6 regions showing interaction between abuse and psychosis from the cortical thickness analysis in the entire sample (section 3.2.2.1) that survived the $p < 0.05$ FWE threshold. I correlated the cortical thickness of these regions with the measures of the HPA axis activity (cortisol levels during the day, CARg and CARi) in cases and controls separately. Among them the right cuneus, latero orbitofrontal gyrus, superior frontal and inferior parietal gyrus were significantly negatively correlated with the cortisol levels during the day while there was no significant correlation with right the post-central and pre-central

¹⁶ I did not correct for multiple comparisons as the four correlations significant at $p < 0.005$ I found it is more than what could be expected just on random chance with a probability of 0.005 in six comparisons.

gyrus in controls (table 2). These correlations were present only among controls as there was no significant correlation between these brain regions and the cortisol levels during the day in cases (table 3.43). Furthermore there was no correlation between these areas nor CARg neither CARi in both controls and cases (table 3.43 and table 3.44)¹⁷.

Brain region	Cortisol level during the day	CARg	CARi
Right hemisphere			
Cuneus	r = -0.48; p = 0.003	r = -0.22; p = 0.19	r = -0.14; p = 0.9
Latero orbitofrontal gyrus	r = -0.45; p = 0.005	r = -0.26; p = 0.9	r = 0.3; p = 0.8
Superior frontal gyrus	r = -0.59; p < 0.001	r = -0.28; p = 0.1	r = 0.08; p = 0.6
Inferior parietal gyrus	r = -0.43; p = 0.008	r = -0.16; p = 0.3	r = 0.49; p = 0.7
Post -central gyrus	r = -0.19; p = 0.2	r = -0.43; p = 0.8	r = -0.24; p = 0.02
Pre-central gyrus	r = -0.24; p = 0.8	r = -0.14; p = 0.4	r = -0.24; p = 0.02

Table 3.43: Correlation between HPA axis activity and cortical thickness in areas showing significant interaction between abuse exposure and presence of psychosis (controls)

Brain region	Cortisol level during the day	CARg	CARi
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¹⁷ I did not correct for multiple comparisons as the six correlations singificative at p<0.005 I found it is more that what could be expected just on random chance with a probability of 0.005 in eighteen comparisons.

Right hemisphere			
Cuneus	$r = -0.08; p = 0.5$	$r = -0.27; p = 0.8$	$r = -0.21; p = 0.1$
Latero orbitofrontal gyrus	$r = -0.12; p = 0.3$	$r = -0.01; p = 0.9$	$r = 0.21; p = 0.1$
Superior frontal gyrus	$r = -0.10; p = 0.4$	$r = -0.04; p = 0.7$	$r = 0.023; p = 0.1$
Inferior parietal gyrus	$r = -0.11; p = 0.4$	$r = -0.02; p = 0.8$	$r = 0.22; p = 0.1$
Post-central gyrus	$r = -0.07; p = 0.9$	$r = -0.02; p = 0.8$	$r = -0.09; p = 0.5$
Pre-central gyrus	$r = -0.24; p = 0.8$	$r = -0.07; p = 0.6$	$r = -0.14; p = 0.3$

Table 3.44: Correlation between HPA axis activity and cortical thickness in areas showing significant interaction between abuse exposure and presence of psychosis (cases).

3.4.3. Cortical thickness and Hypothalamic-Pituitary-Adrenal axis activity in brain regions different between cases with and without history of abuse

Four regions from the cortical thickness analysis comparing cases with and without history of abuse (section 3.2.2.3) survived the correction for multiple comparisons ($p < 0.05$ FWE). There was a significant negative correlation between cortisol level during the day and the right medial orbitofrontal gyrus whereas the other brain regions were not significantly correlated (table 3.45) Similarly the CARi was negatively correlated with the right medial orbitofrontal gyrus unlike the other regions. There was no significant correlation between the CARg and the areas different in cases exposed and not-exposed to abuse (table 3.45)¹⁸.

¹⁸ I did not correct for multiple comparisons as the two correlations significant at $p < 0.005$ I found it is more than what could be expected just on random chance with a probability of 0.005 in fifteen comparisons.

Brain region	Cortisol level during the day	CARg	CARi
Right hemisphere			
Medial orbitofrontal gyrus	$r = -0.33; p = 0.01$	$r = -0.04; p = 0.7$	$r = -0.31; p = 0.02$
Superior frontal gyrus	$r = -0.10; p = 0.4$	$r = -0.02; p = 0.9$	$r = 0.23; p = 0.1$
Inferior parietal gyrus	$r = -0.07; p = 0.6$	$r = -0.01; p = 0.9$	$r = 0.08; p = 0.1$
Pre-central gyrus	$r = -0.43; p = 0.008$	$r = -0.16; p = 0.3$	$r = 0.49; p = 0.7$
Cuneus	$r = -0.06; p = 0.6$	$r = -0.01; p = 0.9$	$r = -0.24; p = 0.1$

Table 3.45 Correlation between HPA axis activity and cortical thickness in areas thinner in cases with abuse exposure than cases without history of childhood abuse.

4. Discussion and Conclusion

“Results rarely specify their causes unambiguously...
if we are forced to infer a process only from its modern results,
then we are usually stymied or reduced to speculation about probabilities.
For many roads lead to almost any Rome”

Stephen Jay Gould¹⁹

¹⁹ The Panda's Thumb, W.W. Norton & Co, 1990

Discussion overview

The findings of this thesis show that the exposure to abuse during childhood has an impact on the brain structure as well as on the HPA axis activity, and that the effects are different in cases and controls.

1) More specifically regarding the brain structure:

- a) As stated in hypothesis 1, childhood trauma was associated with specific abnormalities in the brain. More specifically, smaller grey matter volumes and reduced cortical thickness were identified in the frontal and occipital brain regions in individuals with exposure to childhood abuse, irrespective of the presence of psychosis.
- b) Partly in contrast with hypothesis 1 and hypothesis 2, the brain abnormalities present in controls with history of childhood abuse were not similar to those found in cases with history of childhood abuse but less pronounced. Indeed areas sensitive to abuse in frontal and parietal regions showed greater grey matter volume and cortical thickness in healthy controls than in cases exposed to childhood abuse.
- c) In line with hypothesis 1, childhood abuse was associated with brain abnormalities in both patients and controls. Patients exposed to childhood abuse in comparison with those not exposed showed alterations (smaller grey matter volumes and reduced cortical thickness) in frontal and parietal brain regions. Healthy controls exposed to childhood abuse in comparison with those not

exposed showed changes (greater grey matter volumes and increased cortical thickness) in frontal and parietal regions.

- d) As stated in hypothesis 3 there were gender differences: male individuals with abuse presented more alterations in brain structure in the frontal lobes than female participants with history of abuse exposure in childhood. Furthermore exposure to childhood abuse was associated with abnormalities in cortical thickness in female participants but not among males.

2) Regarding the HPA axis activity:

- a) In contradiction with hypothesis 1, individuals exposed to childhood abuse in comparison with those not exposed did not show alterations of the HPA axis activity.
- b) Controls with history of childhood abuse did show abnormal HPA axis activity when compared with individuals without such history. However, in partial contradiction with hypothesis 1 and hypothesis 2, these abnormalities were not of a magnitude intermediate between cases and controls without abuse exposure. Specifically The Cortisol Awakening Response with respect to the ground (CARg) had a different profile between healthy controls and cases depending on the different levels of abuse exposure (i.e. no abuse, mild abuse, moderate abuse, and severe abuse). The CARg was blunted for mild and moderate abuse and higher for severe abuse among controls and was blunted for severe abuse and higher for moderate among cases.
- c) In line with hypothesis 1, childhood abuse was associated with a pattern of abnormal HPA axis activity in patients as well as in controls. Patients exposed to childhood abuse in comparison

with those not exposed showed a different profile of the CARg for the different levels of abuse exposure (i.e. blunted CARg for severe abuse and higher for moderate abuse). Controls exposed to childhood abuse showed blunted CARg for mild and moderate abuse and higher CARg for severe abuse when compared with individuals without a history of childhood abuse.

- d) As stated in hypothesis 3, the CARg had a different profile in male individuals with exposure to abuse in comparison with those not exposed depending on the different levels of abuse exposure (i.e. mild abuse, moderate abuse, severe abuse). The CARg was not significantly different in female participants with and without childhood abuse exposure. Both female and male cases had a different Cortisol Awakening Response with respect to the ground depending on the different levels of abuse exposure (i.e. no abuse, mild abuse, moderate abuse, severe abuse). Female cases showed a positive correlation between the age at the time of abuse and the Cortisol Awakening response with respect to the increase.

3) Regarding the integration between the brain structure and the HPA axis activity:

- a) As stated in hypothesis 4, cortical thickness of frontal and parietal regions sensitive to abuse exposure were negatively correlated with cortisol levels. Somewhat surprisingly this negative correlation was observed in controls but not in cases.

In this chapter, after an overview of the sample's characteristics (4.1 Overview Socio-demographic Characteristics, Abuse Exposure, and Clinical features in the entire samples) I will discuss the results and their implications by focusing first on the abnormalities in grey matter volume and cortical thickness in

participants with and without history of physical and sexual childhood abuse (4.2. Childhood abuse and brain structure), then moving on to the alterations in cortisol production in individuals exposed to different levels of abuse (4.3. HPA axis activity and childhood abuse), and lastly discussing the findings on the relationship between cortisol secretion and brain structure (4.4. Brain structure, HPA axis activity and childhood abuse). I will then discuss the limitations of the study (4.5. Limitations). The chapter is completed with my overall interpretations of the results and possible future directions for this research (4.6 Conclusion).

4.1 Overview socio-demographic characteristics, abuse exposure, and clinical features in the entire samples

Socio-demographic characteristics of the sample

Patients included a higher proportion of males when compared to healthy controls. Furthermore, they were characterised by a smaller network of social relationships, in terms of support from friends and being in a steady relationship, by lower levels of education and lower proportion of people being in full-time occupation than healthy controls. These differences are consistent with the well replicated findings of a higher prevalence of psychosis among male (Iacono and Beiser 1992; Ochoa et al. 2012); similarly a low level of social support and reduced social functioning have been consistently reported in psychosis and are thought to be a risk factors for the development of the illness, as well as the consequence of the illness onset (Norman et al. 2005; Morgan et al. 2010).

Childhood abuse exposure in cases and controls

The prevalence of childhood physical and sexual abuse was higher among cases than controls (53.2% and 48.6% respectively); furthermore, cases had reported significantly more episodes of severe abuse than their healthy counterparts. These data replicate studies and meta-analyses that consistently identified childhood abuse exposure as major risk factor for the development of psychosis later on in life (Fisher et

al. 2009; Varese et al. 2012; Bonoldi et al. 2013; Bebbington et al. 2014). Indeed, the higher prevalence of more severe abusive experiences among individuals with psychosis is thought to be a key factor in the development of psychosis, along with the overall greater prevalence of abuse (Fisher et al. 2009; Varese et al. 2012; Bonoldi et al. 2013; Bebbington et al. 2014). Despite not being an epidemiological sample, the prevalence of abuse and the characteristics of the severity of the abusive experiences reported are in line with findings from the literature. The proportion of healthy individuals with a history of childhood abuse in my sample is higher than what has been reported by other studies (Fisher et al. 2009; Varese et al. 2012; Bonoldi et al. 2013; Bebbington et al. 2014). However, this finding is related to the fact that I actively recruited healthy individuals who experienced either moderate or severe abuse in childhood to balance the numerosity of the case and controls groups used in the neuroimaging analysis. Nonetheless, this may also be a more realistic estimate of the childhood abuse prevalence in a healthy population due to the use of a face-to-face interview instead of self-reported questionnaires to investigate abusive experiences. This type of assessment is considered the gold standard in exploring traumatic experiences, as the interviewer may help the interviewee to appropriately recognise experiences that could otherwise go unnoticed (Bifulco et al. 1994; Bifulco et al. 2005). Considering the impact of gender on the abuse distribution, male cases showed a significantly higher prevalence of childhood abuse as well as a higher proportion of more severe abuse than healthy controls: these data are consistent with findings in the literature (Fisher et al. 2009; Varese et al. 2012; Bonoldi et al. 2013; Bebbington et al. 2014). Interestingly, female cases had been significantly more exposed to severe abuse than their healthy female counterparts, but the difference in the overall prevalence of childhood abuse in the two groups was not statistically significant. This is in line with evidence showing that in the general population girls are almost three times more exposed than boys to either physical or sexual abuse (Gilbert et al., 2009). Therefore the lack of statistically significant difference in the prevalence of abuse between female cases and female controls may reflect the greater presence of abuse among the general female population. Consistently with the literature, I found that among female participants with psychosis there was a higher proportion of

childhood severe abuse (Fisher et al. 2009; Fisher et al. 2010; Varese et al. 2012; Bonoldi et al. 2013; Bebbington et al. 2014). This, that the risk association between psychosis and severe experiences of abuse in childhood and not the prevalence of childhood abuse in itself, may confirm a dose response effect of abuse in increasing the risk of psychosis (i.e. the more severe the experience the higher the likelihood of having psychosis).

Clinical characteristics

PANSS and physical and sexual abuse

Cases with a history of childhood abuse had higher scores in the total PANSS and in the general symptoms subscale than cases without childhood abuse exposure, these results were driven by the group with moderate abuse exposure. Furthermore, cases without history of abuse exposure have lower PANSS score in the positive symptoms subscale than cases with either mild, severe, or no abuse exposure, this difference is close to significance. Previous studies have identified a history of childhood abuse as a risk factor for experiencing psychotic symptoms in adolescence, and positive correlations have been reported between the severity of the traumatic experiences and positive symptoms in FEP and patients with chronic schizophrenia (Uçok and Bıkmaz 2007; Kelleher et al. 2008; Berg et al. 2014). My findings are partially in line with those results, as the association between abuse and higher PANSS scores was driven by the cases reporting history of moderate abuse. It is possible that above a certain level of intensity, the exposure to childhood abuse ceases to elicit an increase in symptoms intensity so the effect of abuse may be stronger for moderate abusive experiences than for the severe ones. As none of the previous studies

have categorised abuse exposure into different levels, this hypothesis needs to be tested in further research.

There were no differences in the treatment required by patients with different severity of abuse, with no difference in the total dose of antipsychotic medication, measured as chlorpromazine equivalent, across the different level of abuse exposure (i.e. no abuse, mild abuse, moderate abuse and severe abuse). Similarly, a history of childhood abuse was not associated with a significant difference in the severity of the illness and in the mean DUP. Unlike other mental health diseases like depression, little is known about the impact of traumatic experiences on the course of psychosis; using these broad clinical measures (DUP and total exposure to antipsychotic medication), I found no effect of abuse (Heim et al., 2010). My sample comprised individuals at first episode psychosis recruited within three months of their first contact with the mental health services. All the cases had been exposed to low levels of antipsychotic medications; therefore the low level of variation among them (ceiling effect) may explain the lack of differences between cases with and without history of childhood abuse. The DUP in cases with no exposure had a very high standard deviation, higher than in the case of the levels of abuse exposure (i.e. mild, moderate, severe abuse) this could have reduced the possibility of reaching the statistical significance for a difference in mean DUP length relatively large between cases with and without history of abuse. Aside the reduced specificity of the variables used, it is worth considering that the first episode of psychosis is a rather fluid state of the illness with high levels of remissions and change of symptoms over a relatively short period of time. Therefore, it cannot be ruled out that the effect of childhood abuse may become apparent later on in the trajectory of the disease, when the clinical characteristics are more established (Malla et al., 2006).

In summary, my sample replicates most of the findings of studies with individuals at first episode of psychosis, in terms of social characteristics, childhood abuse distribution and clinical profile. Therefore

my sample can be considered representative of the populations present in the catchment area and more in general of the populations (individuals with abuse and patients at first episode of psychosis) object of this study.

4.2. Childhood abuse and brain structure

In this section I will focus on the abnormalities in grey matter volume and cortical thickness in participants with and without a history of physical and sexual childhood abuse. I will first interpret the alterations in grey matter volume and cortical thickness from the analysis exploring the impact of childhood abuse exposure on brain structure in the entire sample (4.2.1 Effect of physical and sexual abuse in childhood on brain structure), then on the similar analyses conducted in men and women separately (4.2.2 Gender differences in the effect of abuse on the brain structure). In each section I will describe the results of each comparison first and then propose an interpretation of the findings (4.2.1.6 What the structural differences between individuals with and without physical and sexual abuse can reflect and 4.2.2.4 Overview of the gender differences on the effect of childhood abuse on brain structure).

Finally this section will close with the discussion of the results on the effect of psychosis on the grey matter volume and cortical thickness in the entire sample (4.2.3 Effect of psychosis on brain structure) followed by an analysis on men and women separately (4.2.3.2 Gender differences on brain structure in individuals with psychosis).

In this section individuals without history of childhood abuse exposure were compared with individuals exposed to moderate-severe physical and sexual abuse (for more details see section 2.2.3 Coding of childhood exposure for structural MRI analysis). Lastly, in this section I will discuss grey matter volume differences when significant at $p < 0.05$ FWE, or those that did not survive the more conservative FWE

correction but were significant at $p < 0.001$ uncorrected and had a cluster size of 100 voxels; cortical thickness differences were discussed only when significant at $p < 0.05$ after correction for multiple comparisons (for more details see section 2.2.5.3.3 Reporting results for VBM analysis and 2.2.4.3.3 Reporting results for FreeSurfer analysis).

4.2.1 Effect of physical and sexual abuse in childhood on brain structure

In my study a wide range of brain structural alterations emerged in the frontal, limbic and occipital lobes in relation to the effect of abuse, irrespective of the presence of psychosis. Individuals with abuse exposure showed a reduction in the grey matter volume in the left insula, left superior and medial frontal gyrus as well as the anterior cingulate bilaterally, all significant at $p < 0.001$ uncorrected with a cluster size of 100 voxels. When I examined cortical thickness, I found that the presence of abuse was associated with cortical thinning of the right medial orbitofrontal gyrus and of the right lingual gyrus, significant at $p < 0.05$ FWE corrected. Furthermore, the precuneus showed larger grey matter volume in controls with abuse, compared to controls without abuse, while it was smaller in patients with abuse than in patients with no abuse, significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels. Controls with abuse showed greater cortical thickness in the right cuneus, right lateral orbitofrontal gyrus, right superior frontal gyrus, right inferior parietal gyrus, right post-central gyrus and right pre-central gyrus, compared to patients with abuse. These were significant with a $p < 0.05$ FWE.

4.2.1.1 Differences in brain structure between individuals with and without physical and sexual abuse in childhood

I found that a history of physical and sexual abuse in childhood was associated with smaller grey matter volume in the left insula, in the left superior and medial frontal gyrus and in the anterior cingulate bilaterally. Furthermore, I found that abuse is associated with thinning of the right medial orbitalfrontal gyrus and of the right lingual gyrus.

These areas, with the exception of the lingual gyrus, are thought to be implicated in higher order emotional and cognitive processes; these functions are often impaired in individuals with history of childhood maltreatment (Tau and Peterson 2010; Lim et al. 2014). Conveying autonomic and visceral information as well as motor, somatosensory and vestibular input, the insula has an important role in heteromodal sensory integration and is central to learning processes, motivation and language expression through its connections with cortical and subcortical structures (Flynn 1999; Ochsner and Gross 2005). The superior and medial frontal gyrus, as well as the cingulate, are similarly important in exerting control over emotions and in the activation of working memory (Ochsner and Gross 2005; Boissgueheneuc et al. 2006). Consistently with my results, alterations in these regions are often reported as consequences of different types of abuse (Compton 2003; Hart and Rubia 2012). Grey matter volume is often reported as smaller in the amygdala and hippocampus of individuals with history of childhood abuse. Somewhat surprisingly, I found no association between these regions and the abuse exposure (Hart and Rubia 2012). The amygdala and the hippocampus have usually been studied with a region of interest approach and interestingly, none of the few existing whole-brain VBM studies have reported hippocampal or amygdala differences between individuals with and without abuse exposure.

Although the reduction of grey matter volume in the right orbitofrontal cortex is a well-replicated finding in the general population, and the thinning of this area has been found in children exposed to abuse, this is the first study to show a reduction in its cortical thickness in adults with trauma exposure (De Brito et al. 2013; Kelly et al. 2013; Lim et al. 2014). Similarly to other regions displaying grey matter volumes abnormalities in my sample, the right orbitofrontal cortex is anatomically and functionally connected to brain structures mediating emotion regulation, cognitive flexibility and decision-making processes (Cavada and Schultz 2000; Kelly et al. 2013). Structural alterations in fronto limbic areas, such as the insula, the anterior cingulate, the superior and medial frontal gyrus and the orbitofrontal gyrus are consistently associated with exposure to traumatic experiences in childhood (Hart and Rubia 2012). These circuitries are pivotal in the top-down regulation of the behavioural response to emotively charged stimuli. Therefore, the presence of these structural alterations could explain deficit in emotional control, attention regulation and emotion discrimination that are often reported in adults and children with a history of early maltreatment (Hart & Rubia, 2012). As they complete their development in late adolescence, these areas are characterised by a longer window of development than unimodal brain regions, and are therefore more susceptible to negative external stimuli (Toga, Thompson, & Sowell, 2011). Quite differently from these areas, the lingual gyrus is a unimodal sensory area, important in figure recognition and object naming (Macaluso, Frith, & Driver, 2008). This is the first time that this area has been found thinner in a mixed-gender sample exposed to childhood abuse. Alterations of its cortical thickness have been previously associated with either physical or sexual abuse in women. Nonetheless, it is not completely clear why a sensory area should be affected by exposure to abuse (Tomoda et al., 2009). Abnormalities of the sensory system that relay adverse sensory experiences have been linked with the experience of abuse at an early age (Tomoda et al. 2012; Lim et al. 2014). The reduction in cortical thickness of these regions, or volume for that matter, has been thought to reflect an adaptive mechanism

that protects the child by sensory gating the abusive experience (Teicher et al. 2006; Tomoda et al. 2012; Lim et al. 2014).

It is increasingly recognised that the adult brain is organized into structural and functional networks that carry out higher order functions more efficiently (Martin H. Teicher et al., 2014). The way different parts of the brain are interconnected to each other has been successfully approximated to a network whose nodes are discrete brain regions, and the nodes with the highest number of communications, therefore central in the structure of the system, are called hubs (Bullmore et al., 2009). Interestingly, individuals with a history of childhood abuse show a different network morphology that individuals with no-exposure (Cisler et al. 2012; Teicher et al. 2014). Critically, the left anterior cingulate, the middle frontal gyrus and the prefrontal cortex, hubs in within the network of healthy individuals, show a reduced connectivity in the intra-hemisphere network in those exposed to maltreatment and conversely the right anterior insula and precuneus, that are not important hubs in healthy individuals' network, become hubs in those exposed to childhood maltreatment (Cisler et al. 2012; Teicher et al. 2014). The hubs that lose centrality in the network of people with history of maltreatment are involved in emotion regulation, attention and social cognition, and the areas that acquire centrality are linked with self-awareness. This reconfiguration has lent to propose that these changes may represent an adjustment of brain functions to adapt to abuse exposure (Cisler et al. 2012; Teicher et al. 2014).

4.2.1.2 Interaction between psychosis and abuse exposure

The left precuneus had larger grey matter volume in controls with abuse, while it was smaller in patients with abuse, ($p < 0.001$ uncorrected with a cluster size of 100 voxels). Similarly, controls with abuse showed greater cortical thickness in the right cuneus, lateral orbitofrontal gyrus, superior frontal gyrus, inferior parietal gyrus, post-central and pre-central gyrus, compared to patients with abuse. These were significant with a $p < 0.05$ FWE.

The presence of an interaction between psychosis and abuse is suggestive of a different impact of the abuse exposure in individuals with and without psychosis. Interestingly, it the first time a differential effect of childhood abuse on the structure of the brain has been reported. Childhood maltreatment has been associated with altered development of the sensory system that convey traumatic sensory experience (Lim et al., 2014). Indeed, the post-central gyrus, the primary somato-sensory cortex, has been previously found altered in relation to childhood maltreatment (Lim et al., 2014). Apart from the pre-central and post-central gyrus, the other areas showing an interaction between psychosis and childhood abuse are regions characterised by complex cognitive functions, requiring the integration of somato-sensory information involved in cognitive flexibility, and completing development into late adolescence (Flynn 1999; Price 2000; Rubinstein et al. 2001; Sowell et al. 2003 Ochsner and Gross 2005; Mcewen 2007; Boisgheheneuc et al. 2006). Integration of heteromodal information, involvement in higher cognitive functions as well as a long period of maturation are features often reported of areas affected by exposure to adverse environment (Flynn 1999; Price 2000; Rubinstein et al. 2001; Sowell et al. 2003 Ochsner and Gross 2005; Mcewen 2007; Boisgheheneuc et al. 2006). It has been found that the latero orbitofrontal cortex, the superior frontal cortex, the cuneus and precuneus, as well as the pre-central gyrus and inferior parietal gyrus, are involved in the cognitive flexibility needed to adapt to novel circumstances (De Baene,

Albers, & Brass, 2012). The latero orbitofrontal cortex, the superior frontal cortex the cuneus and precuneus are activated during the process of setting goals when confronting a new situation and the pre-central gyrus and inferior parietal gyrus are activated during the elaboration of the behavioural outcomes to reach those goals (De Baene et al., 2012). It is suggestive that the exposure to childhood abuse is linked with the brain regions involved in the cognitive flexibility needed to adapt to novel circumstances, a function that can determine a positive or negative, or rather more or less stressful, interaction with the environment (Rubinstein et al. 2001).

The alterations in the structure of these regions, dissimilar between cases and controls, with possibly a less adaptive structure in cases, may be consistent with the literature on the cognitive characteristics of patients with psychosis. For example, reduced cognitive flexibility is a well-defined aspect of the cognitive deficit present in individuals with psychosis (Delahunty et al. 1993; So et al. 2012). Furthermore the right cuneus, right latero orbitofrontal gyrus, right superior frontal gyrus, right inferior parietal gyrus, right post-central gyrus and right pre-central gyrus, known to be thinner in psychosis, are associated with more severe psychotic symptoms and cognitive dysfunction (Oertel-Knochel et al. 2013; Xiao et al. 2015). Deficit in brain functions (e.g. working memory, cognitive flexibility) are thought to facilitate the emersion of psychiatric symptoms and brain regions abnormalities are often associated cognitive deficits, additionally the simultaneous presence of cognitive deficits and brain structure abnormalities seems to predispose to the development of symptoms (Delahunty et al. 1993; So et al. 2012; Oertel-Knochel et al. 2013; Xiao et al. 2015). I have found that exposure to abuse in childhood is associated with specific alterations in the architecture of these regions in individuals with psychosis. Challenging the brain to adapt to the environment, childhood abuse could undermine the brain architecture in vulnerable individuals and thus facilitate the development of some of the cognitive deficits present in psychosis as well as psychiatric symptoms (Delahunty et al. 1993; So et al. 2012). The higher

scores at the PANSS (i.e. general symptoms, total PANSS score) shown by these patients in my sample may express this relationship.

If the reduction of thickness and volume, which often reflects an abnormal neuronal structure, in brain regions linked with altered cognitive functions in psychosis seems plausible in presence of history of childhood abuse, it is not obvious what greater a volume and thickness in the same regions in healthy individuals with exposure to childhood could reflect (Smiley et al. 2012; Williams et al. 2013). Increased grey matter volume has been associated with increased activity in brain areas (Adler et al. 2005; Cisler et al. 2012; Teicher et al. 2014). In addition, changes in brain structure have often been proved to be coupled with a reorganisation of brain function (Adler et al. 2005; Cisler et al. 2012; Teicher et al. 2014; Xiao et al. 2015). Interestingly, animal models have shown that a rise in the adrenergic and glucocorticoid activity resulting from exposure to chronic stress is coupled with the expansions of the dendritic structure in neurons in the orbitofrontal cortex, to sustain increased vigilance (Radley et al. 2004; Mcewen et al. 2015). As result of the reorganisation of functions induced by traumatic experiences, these areas may have increased their activation, for example when individuals were adapting to new situations, thus developing greater volume and thickness in resilient individuals (Teicher et al. 2014; Xiao et al. 2015). This type of modification may be suggestive of adaptive changes in the brain architecture in resilient individuals (healthy controls with abuse exposure).

4.2.1.3 Differences in brain structure in patients with and without a history of physical and sexual childhood abuse

I found that cases with a history of sexual and physical abuse in childhood display a volume reduction in the right anterior cingulate, significant at $p < 0.05$ after FWE correction. Individuals with psychosis and history of abuse also showed an increase in cortical thickness in the left pre-central gyrus and thinning of the cortex in the right superior frontal gyrus, right medial orbitofrontal gyrus, right inferior parietal gyrus and right cuneus, significant at $p < 0.05$ after FWE correction.

These areas are known to be abnormal in individuals with childhood abuse exposure and the findings confirm a pattern of vulnerability for regions involved in higher order emotional and cognitive processes characterised by a long window of development (Teicher et al. 2006; Lim et al. 2014; McEwen et al. 2015). Furthermore, abnormalities in these regions are well replicated in the FEP literature and for most of them the magnitude of the abnormality is proportional to the severity of psychotic symptoms (Fornito et al. 2009; Oertel-Knochel et al. 2013; Xiao et al. 2015). As abnormalities in brain regions seem to predispose to the development of psychiatric symptoms, these alterations in cases exposed to childhood abuse when compared with not-exposed cases may help explain the worse symptomatology showed by those patients.

The thicker left pre-central gyrus it is not a common finding in individuals with childhood exposure to abuse on the contrary it has been found to be thinner in FEP when compared with healthy controls (Xiao et al., 2015). I showed that cases and controls differed in the thickness of the right pre-central gyrus and this finding is somewhat surprising. It is rather common to find thicker brain regions in individuals recently diagnosed with affective or non-affective psychosis, and this is thought to be a compensatory

mechanism present at the beginning of the illness, which may disappear in time (Schultz et al. 2010b; Xiao et al. 2015). Therefore, this finding may be related to a short illness duration (Schultz et al. 2010b; Xiao et al. 2015). As this area is also part of a network of regions involved in cognitive flexibility, and since I found changes in the structure of the right pre-central gyrus associated with history of abuse, the increased thickness may be the consequence of biological and functional changes induced by the abuse exposure (Teicher et al. 2006; Lim et al. 2014; McEwen et al. 2015). The presence of childhood abuse seems to describe a group of FEP individuals with specific, worse, clinical features. In line with the presence of higher score for the PANSS subscale general psychopathology and total PANSS score in individuals reporting history of abuse in my sample. Indeed childhood abuse could destabilise the brain architecture in vulnerable individuals facilitating the emersion of some of the cognitive characteristics present in psychosis as well as psychiatric symptoms (Delahunty et al. 1993; So et al. 2012).

4.2.1.4 Differences in brain structure in healthy controls with and without a history of physical and sexual childhood abuse

Controls with history of physical and sexual showed a smaller grey matter volume in the left middle frontal gyrus, significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels.

The left middle frontal gyrus has been commonly reported as altered in individuals with history of abuse, and this finding confirms the pattern that has been emerging in my study and in the literature of association of complex brain regions involved with higher order cognitive function, most notably working memory, with abuse exposure (Boisgucheneuc et al. 2006; Lim et al. 2014). This area has shown abnormal activation in individuals with early traumatic experiences during a working memory task;

however, this abnormal activation does not translate into a worst performance in terms of accuracy. Consequently this change may promote the maintenance of normal function also in individuals exposed to abuse (McCrory et al. 2010; Edmiston et al. 2011; De Brito et al. 2013; Philip et al. 2015). The small number of areas different between healthy controls with and without history of abuse, just one in fact, may indicate a more subtle effect of abuse on controls which can be detected only in bigger sample (M. H. Teicher et al., 2012). Most of the areas known to be smaller in individuals with history of abuse (i.e. amygdala, hippocampus, frontal regions) result from sample with individuals with psychiatric conditions (Lim et al. 2014; Hart and Rubia 2012). Interestingly when samples with only healthy individuals has been used or these conditions had been accounted for, the effect size of the abuse exposure has considerable reduced and some areas, most notably amygdala and hippocampus, have not been replicated (Lim et al. 2014; Hart and Rubia 2012). The small effect size I have found in a comparison between exposed and not-exposed individuals without psychiatric condition reflects this tendency and may detect the real effect of childhood abuse in the healthy population.

4.2.1.5 Biological substrata of grey matter volume and cortical thickness alterations in individuals exposed to physical and sexual abuse

Grey matter volume is a composite measure influenced by variation in cortical thickness, grey matter folding and surface area, and is therefore difficult to draw conclusions on the biological alterations that underlie it (Schultz, Koch, Wagner, Roebel, Schachtzabel, et al., 2010). Nonetheless a reduction in neuronal density has been consistently reported in healthy individuals with decreased grey matter volume, suggesting that this reduction of neurons could be one of reasons for the volume modifications detected (Harrison and Harrison 1999; Raz 2005). Changes in thickness have been consistently linked with

variations of the architecture of the cortical layers mainly due to modifications of the dendritic and axonal branches of the pyramidal cells particularly in layer II/III and V (Ziegler et al., 2012). Connections between grey matter volume variations and neuronal density as well as cortical thickness changes and modifications of neuronal dendritic and axonal branches have been consistently found in parietal and frontal lobes of individuals with psychosis and schizophrenia (Schultz et al. 2010a; Smiley et al. 2012; Williams et al. 2013). As the more important mediators of the response to environmental stressors (i.e. glucocorticoids and catecholamines) are known to alter neuronal architecture and density, these may be some of the biological mechanisms underling the structural modifications I have found in cases as well as in controls in relations to childhood exposure to abuse.

An increase in glucocorticoid concentration occurs in response to a stressor. This is associated with a reorganization of the neuronal structure, a reduction and loss of apical dendrites and the inhibition of cellular proliferation (de Kloet et al., 2005). Since during the stress response there is a rise in excitatory neurotransmission (e.g. glutamatergic), the retraction of peripheral dendrites from excitatory toxicity protects the neurons (Lupien et al., 2009). In contrast, an abnormal secretion of glucocorticoid hormones, either too high or too low, ceases to protect neurons and rather produces detrimental effect in areas rich in glucocorticoid receptors (i.e. hippocampus, frontal cortex and amygdala) (McEwen et al. 2015). Indeed too high or too low glucocorticoid concentrations have been associated with retraction of dendrites, reduction of the synapses density, impairment of cellular turnover and rise of neuronal apoptosis (McEwen et al. 2015). As cortisol increases the release of glutamate, its effect can be independent of the binding of glucocorticoid receptors; higher glucocorticoid secretion has been linked with a stress-induced remodelling of dendrites and synapses, as well as with excitatory toxicity in the hippocampus and in the frontal and prefrontal cortex, leading to loss of neurons and changes in activation and length of neuronal circuitry (Arnsten 2015; McEwen et al. 2015). The other important class of stress mediators, catecholamines, have a dose-response effect as well; at lower concentrations they promote the activation

of the pre-frontal cortex, stimulating a top-down regulation of thoughts, actions and emotions (Arnsten 2015). Over time, an unregulated catecholamine secretion can increase the activity of some neuronal circuitries over others, for example at high catecholamine levels, there is a reduction in activation of the prefrontal cortex and an increase of the amygdala and the basal ganglia (Arnsten 2015). This has been associated with a reduction in synapse density and an overall volume of the dorsolateral prefrontal cortex and the ventral and medial prefrontal cortex and a parallel increase in volume of the amygdala (Arnsten 2015; McEwen et al. 2015). Glucocorticoids and catecholamines can also affect each other in the short as well as in the long term: the coordinated pharmacological stimulation of glucocorticoids and adrenergic receptors has been proven to activate the orbitofrontal and medial prefrontal cortices, disrupting dendritic branching as well as goal directed behaviour (Radley et al. 2004; Schwabe et al. 2012; McEwen et al. 2015). In contrast, chronic stress exposure, with increased secretion of glucocorticoids and catecholamine, has been associated with cognitive rigidity and expansion of orbitofrontal cortex dendrites (Radley et al. 2004; Schwabe et al. 2012). Furthermore exposure to physical and sexual abuse has been linked with increased and sustained activation of the stress response systems and therefore it is plausible to hypothesise that these mechanisms play a part in the changes in grey matter volume and cortical thickness found in individuals with history of abuse.

It is difficult to determine whether changes related with the exposure to childhood abuse are always detrimental. The smaller volume and thinner cortices found in my analysis (section 4.2.1.2 and section 4.2.1.2) could be the result of a reorganisation of dendrites and synapses that reduces neuronal surface. This allows an adjustment to an adverse environment preventing excitotoxicity and promoting the development of some neuronal circuitry over others.

The differences in brain architecture between cases and controls with a history of abuse (Section 3.2.1.1 page 131 and section 3.2.2.1 page 153) could be explained by differences in the biological milieu where

the stress response takes place. The two groups could require different level of adaptation to the environment, and differences in protective and vulnerability factors across the groups could result in a different impact of the childhood abuse on the brain. Interestingly most of the more consistent biological abnormalities found in individuals with psychosis are related with alterations in the way the brain reacts to stress exposure, these vulnerabilities could play a part in the different alterations I found in cases and controls (Mondelli et al. 2011; Sapolsky 2015; Toll and Mané 2015).

The Brain-Derived-Neurotropic-Factor (BDNF) stimulates neuronal growth and maturation; moreover it has been proposed to have a protective effect against the detrimental plasticity induced by stress (i.e. increment of the proximal dendrites, reduce synapses density, reduce neuronal growth, increase of apoptosis). Interestingly, individuals at first episode of psychosis have been found to have reduced levels and gene expression of BDNF (Mondelli et al. 2011; Toll and Mané 2015). The importance of BDNF in individuals with psychosis to mitigate the consequences of an adverse environment has been recently shown (Aas et al., 2013). Among individuals with schizophrenia, a genetically determined lower secretion of BDNF and exposure to physical childhood abuse is associated with significantly poorer cognitive function than those patients with the same history of abuse exposure but a normal production of BDNF (Aas et al., 2013). Similarly in case of exposure to severe childhood sexual abuse individuals with schizophrenia and low BDNF production show a smaller right hippocampal volume than those patients with comparable history of sexual abuse but normal secretion of BDNF (Aas et al., 2013). Another suggestion of the importance of the stress response in schizophrenia is given by the Disrupted In Schizophrenia 1 (DISC1) and the Catechol-O-methyltransferase (COMT); two important candidate genes for psychosis that, in their abnormal variants, have the potential to harmfully amplify the adrenergic activation to stress (Castro-catala et al. 2015; Arnsten 2015). DISC 1 is a scaffolding protein expressed in the layer III of the prefrontal cortex and important in anchoring the phosphodiesterases used for the intracellular stress signalling (Camargo et al., 2007). Alterations in the protein, especially in presence of

increased levels of inflammation, can reduce the ability of DISC 1 to anchor the phosphodiesterases, which is thought to be instrumental in disinhibiting the stress response and lowering the threshold for stress induced prefrontal cortex alterations (Arnsten 2015). Individuals with psychosis have been found to have high levels of inflammation and high prevalence of the less functional DISC 1, which can both be involved in a non optimal response to childhood abuse (Arnsten 2015; Bloomfield et al. 2015; Mondelli et al. 2015; Sapolsky 2015). COMT is an enzyme that metabolites catecholamines such as dopamine, adrenaline noradrenaline; a methionine substitution in this catabolic enzyme weakens its ability to degrade its substrates and increases the concentration of adrenaline and noradrenaline therefore the magnitude of the adrenal stimulation in response to stress (Arnsten 2015). Finally glucocorticoid hormones stimulate the cellular response to stress inducing protein synthesis; increases in glucocorticoid induced protein synthesis, and therefore an abnormal reaction to stress, can be the consequence of genetic mutations in the glucocorticoid receptor or in the proteins that promote the translocation of the receptor in the neuronal nucleus (Mcclung, 2015). These mutations are more common among individuals who, after exposure to early stress, develop a mental illness. For example, psychosis has been associated with a genotype characterised by higher prevalence of a mutation of the FKBP52, a mutation that increases the translocation of the glucocorticoid receptor in the nucleus (Sinclair et al. 2013; Fillman et al. 2014; Mcclung 2015).

These genetic abnormalities could singularly or cumulatively help explain differences brain architecture found in patients and controls with a similar history of abuse exposure. Furthermore, as the timing and the intensity of the glucocorticoid production is central for the development of detrimental consequences on the brain (Pruessner et al. 2013a; Pruessner et al. 2013b; Borges et al. 2013a; Mondelli et al. 2010a). Differences between healthy individuals and patients could be explained with the altered HPA axis activity associated with psychosis (Pruessner et al. 2013a; Pruessner et al. 2013b; Borges et al. 2013a;

Mondelli et al. 2010a). An altered HPA axis activity could play its part alone or in conjunction with genetic abnormalities, eventually affecting the stress response.

The abnormalities in grey matter volume and cortical thickness present in psychosis and schizophrenia can be the expression of an accelerated pruning, following a pattern of structural changes that closely resembles the normal development of the brain but which happens earlier on and is of a bigger magnitude (Sun et al., 2009). Consistently with this model individuals at risk of developing psychosis would have an abnormal neuronal development thus the challenge to react to childhood abuse could determine a shift in the quality of a process otherwise adaptive, causing the changes I found in this group of individuals (Mondelli et al. 2010; Mondelli et al. 2011; Garcia-Rizo et al. 2012a; Girgis et al. 2014). This mechanism could also help explain the pattern of brain abnormalities that patients with a history of abuse showed in comparison with patients without such history (4.2.1.3 Differences in brain structure in patients with and without a history of physical and sexual childhood abuse).

If reductions of cortical thickness are thought to be representative of aberrant pruning and apoptosis in the neural structure, it is less clear what are the biological processes behind the increase in thickness (Jarskog et al. 2005; Glantz et al. 2006). One possible explanation is that the cortical thickening may represent a compensative mechanism that is active at the beginning of the illness, which reduces with time to nearly disappear in chronically ill individuals (Xiao et al., 2015). Indeed, increased cortical thickness is more commonly found in individuals recently diagnosed with affective or non affective psychosis than in individual with a chronic disease (Schultz et al. 2010b; Xiao et al. 2015). These abnormalities could also reflect a hypertrophy due to the osmotic changes in the cell that precede apoptotic osmosis, which prompt an increase in thickness before a reduction with the progression of the illness (Adler et al., 2005). Finally, in line with the synaptic pruning developmental model of schizophrenia, thicker areas might be the

consequence of an abnormal pruning which instead of removing too many neurons, leaves synapses and axon branches intact where in turn they should be pruned (Rapoport, Giedd, & Gogtay, 2012).

4.2.1.6 What the structural differences between individuals with and without physical and sexual abuse can reflect

Grey matter volume and cortical thickness are two aspects of brain morphology that relate to each other, as grey matter volume is a function of cortical thickness and cortical surface area. Yet, they are able to convey different pieces of information. Grey matter volume is a global measure of the structure of the brain, and provides information on grey matter without differentiating among its three components (i.e. cortical thickness, surface and folding) (Schultz et al. 2010; Sprooten et al. 2013). Furthermore, cortical thickness, surface and folding contribute unequally to the final measure of volume: indeed, differences in grey matter volume across subjects are largely influenced by the local cortical folding and reflect more closely variation in the surface area than in cortical thickness (Winkler et al. 2010). In contrast, cortical thickness is a one-dimension marker relatively independent of cortical surface area and more related to the cellular layers that compose the human cortex. Abnormalities in cortical thickness have been consistently associated with histological alterations found in post mortem studies of healthy individuals as well as individuals with psychosis (B. Fischl & Dale, 2000). Finally, the spatial resolution of the two measures is different, grey matter volume can detect differences at voxel level (i.e. in this study a cube of 1.02x1.02X1.2mm) whereas cortical thickness can be determined in sub-millimetre dimensions. Used in my study, the two measures have conveyed information on different spatial scales and on different determinants of the brain structure, complementing each other and contributing to a more nuanced understanding of brain architecture associated with abuse exposure.

As stated in hypothesis 1, childhood trauma was associated with specific patterns of brain abnormalities in cases as well as in controls. Interestingly, controls with history of childhood abuse did not show a profile of alterations similar to the cases without history of abuse but less pronounced, in partial contradiction with hypothesis 1 and 2. Explaining the structural alterations present in the frontal, limbic and occipital lobes in individuals with a history of abuse is not straightforward. Even more so when considering that structural MRI studies in individuals with childhood maltreatment very often include individuals with psychiatric conditions, most prominently PTSD mood and anxiety disorders, for which they are very rarely controlled (Teicher et al. 2003; Lim et al. 2014; Hart and Rubia 2012). This limitation is particularly present in volumetric studies where the effect of concomitant conditions is not often taken into account (Hart and Rubia 2012). This is the case for the most recent and comprehensive meta-analysis of whole-brain VBM studies and the effect of childhood trauma. Here, all its 12 studies but 1 included different proportions of participants with psychiatric diseases (Lim et al. 2014; Hart and Rubia 2012). It is very difficult to clarify if the alterations shown are the effect of the early traumatic experiences, the underlying psychiatric condition or a combinations of the two (Teicher et al. 2006; Hart and Rubia 2012; Sapolsky 2015). Indeed, the regions associated with effect of abuse have a wide range of connections, a slow maturation process and are prevalently involved in complex functions; these elements make them vulnerable to the impact of the childhood abuse as well as the intervening psychiatric condition which arise later on in life (Hart and Rubia 2012). The regions where I found an effect of abuse on grey matter volume (section 4.2.1.1 and section 4.2.1.2), although similar to those found in previous literature, did not survive the correction for multiple comparisons. Since I controlled for the effect of psychosis in the analysis, this may have made the effect size of the volume reductions too small to be significant after FWE correction, but not with more liberal, but still informative, combination of threshold and cluster size (i.e. $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels). This might mean that the effect of abuse, once the confounding presence of concurring mental illness is removed, is too

subtle to be detected at voxel level but not when using a smaller resolution, as it the case for the analysis of the cortical thickness (Section 4.2.1.1 and Section 4.2.1.2). Maybe the biological changes induced by the exposure to abuse can modify the structure of the neurones at a layer level in sensitive areas, but not go as far as inducing cellular apoptosis, usually the mechanism underlying reduction in grey matter volume (Schultz et al. 2010b; Xiao et al. 2015). It is interesting to note that a smaller grey matter volume in the insula is often reported in individuals with psychosis, and I found this alteration associated with childhood abuse exposure (Fornito et al. 2009; Fusar-Poli et al. 2012a). Thus, the smaller volume in the insula in FEP could result from the effect of abuse in individuals with psychosis and not represent a distinctive feature of psychosis. This consideration would also explain the lack of result from the ROIs in areas know to be different between individuals with and without childhood abuse exposure. Indeed, the regions were chosen using the meta-analysis from Lim et al. (2014), which also included individuals with psychiatric conditions. It is possible that by removing the effect of psychosis in my analysis I also reduced the chances of identifying differences in these areas. Other reasons for the failure to reach statistically significant threshold after correction for multiple comparisons should be considered. In my sample, abuse exposure had a more pronounced effect on of the brain structure of male than female participants; these different effects on grey matter volume may have balanced each other out in the entire sample analysis (section 4.2.2.1). Finally my sample includes individuals with different ethnic origins. Ethnic variations in the brain abnormalities present in FEP have recently emerged but it is unknown if this is also the case for abuse (i.e. different patterns of brain abnormalities depending on the different ethnicity)(Gong et al. 2015). I controlled for the confounding effect of ethnicity using the ethnical origin of the participants as covariate in the analysis (section 2.2.4.3.1). This may have not prevented the different patterns of brain abnormalities to balance each other out if present. Unfortunately it was not possible to study the effect of childhood abuse on ethnically homogenous sub-samples as the groups for the different levels of abuse would have been to small.

In summary, the abnormalities that I found in grey matter volume (in the left insula, in the left superior and medial frontal gyrus and in the anterior cingulate bilaterally) and cortical thickness (right medial orbitofrontal gyrus and of the right lingual gyrus) in individuals with childhood abuse exposure after controlling for the presence of psychosis, are in areas consistently reported to be affected by childhood maltreatment. However, the implications of these abnormalities are difficult to explain (Hart and Rubia 2012; Lim et al. 2014). While these regions have been associated with abnormal brain activation and cognitive function in individuals reporting a history of abuse, the vast majority of those individuals had psychiatric conditions (Hart and Rubia 2012; Lim et al. 2014). Therefore it is impossible to understand whether the abnormal brain activation and the impaired cognitive functions are a consequence of the childhood abuse exposure, of the psychiatric condition or of a combination of both. Larger cortical volume or greater grey matter density are commonly regarded as proxy for higher computation efficacy and better cognitive ability (Kanai & Rees, 2011). Nonetheless, there are conditions associated with larger and thicker areas of the cortex. These include for example amusia with thicker right inferior frontal gyrus and distractibility with larger superior parietal lobe. Also, cognitive abilities and the computational efficacy normally increase during adolescence, when the brain undergoes an extensive pruning and dramatically reduces its grey matter component thus a stark reduction in grey matter promotes better and more economical brain performances (Huttenlocher and Dabholkar 1997; Kanai and Rees 2011). The structural alterations I found associated with childhood abuse should not necessarily be regarded as dysfunctional per se, since they result from this lifelong process (Toga et al. 2011). During its maturation and throughout the lifespan, the brain changes and adapts itself to the environment, thus this pattern of abnormalities could be the outcomes of architectural changes that improve the brain functioning and adjust the brain to an adverse environment. In line with this interpretation, some studies have linked similar alterations to a structural and functional reorganization of the brain that could be an attempt to preserve normal functioning (Cisler et al. 2012; Teicher et al. 2014). In healthy individuals this pattern of

changes can be considered as the result of a process to adjust to the environment. These findings may highlight regions and mechanisms of resilience in the brain.

Finally, the adaptation to a challenging environment happens with the same spatial distribution in individuals with psychosis and healthy controls, but with different results. Indeed, patients and controls show a different pattern of changes: greater volume and thickness in healthy controls and smaller in FEP. Stress adaptation and recovery do not represent variations around a stress free baseline, they are processes part of each individual's life thus they are influenced by the individual's characteristics. Consequently the more or less successful adjustment to physical and sexual childhood abuse is influenced by the individual's biological and social milieu, in terms of genetic predisposition and stress response (Sun et al. 2009; Tau and Peterson 2010; Mondelli et al. 2011; Garcia-Rizo et al. 2012a; Koutsouleris et al. 2013; Girgis et al. 2014). Accordingly these divergent patterns associated with history of childhood abuse in cases and controls can be the outcomes of the genetic vulnerability that differentiates those you would develop psychosis later on in life from those you would not. Among FEP exposure to childhood abuse seems to determine some clinical characteristics (worse symptomatology) but these brain abnormalities should not be deemed pathognomonic of psychosis. Indeed these regions are abnormal also in people with childhood abuse and other psychiatric conditions, most prominently PTSD, mood and anxiety disorders (Teicher et al. 2003; Lim et al. 2014; Hart and Rubia 2012). These similarities across psychiatric disorders could highlight these regions, characterised by a maturational process that ends in late adolescent and complex neuronal structure, as just areas vulnerable to external stressors and able to play a different role in the brain functioning in healthy controls as well as in people with different psychiatric conditions depending on the overall individual's biological context.

4.2.2 Gender differences in the effect of abuse on the brain structure

In the following sections I am going to discuss the results of the exposure to physical and sexual abuse in childhood in male and female participants separately. The result will be described for each of the comparisons produced (in the entire female sample and then female cases and controls separately, likewise for males the entire male sample followed by male cases and controls separately). These will then be followed by an overview of the characteristics that could be specifically due to gender (4.2.4 Overview of the gender differences on the effect of abuse).

4.2.2.1 Effect of physical and sexual abuse in childhood on brain structure – entire sample - gender differences

When analysed separately, male and female participants showed a wide range of brain structural alterations in relation to exposure to physical and sexual abuse in childhood, which were different in localisation and extension. Comparing female participants with and without a history of abuse showed no differences. When I looked at the cortical thickness, I found that the presence of abuse was associated with a thickening of the right inferior parietal gyrus lateral orbitofrontal gyrus, significant at $p < 0.05$ after FWE correction. Furthermore, the left pericalcarina cortex, right post-central gyrus, right superior frontal gyrus, right superior parietal gyrus, right cuneus and right inferior temporal gyrus, showed larger cortical thickness in female controls with abuse, compared with female controls without abuse, while they were thinner in female patients with abuse than in female patients with no abuse, all results significant at $p < 0.05$ corrected for FWE. Male with history of childhood abuse showed a smaller grey matter volume in

the right anterior cingulate, left paracentral lobule, left superior frontal gyrus, left medial frontal gyrus when compared with male participants without abuse exposure, all significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels. Furthermore, the left medial frontal gyrus showed larger grey matter volume in male controls with abuse and it was smaller in male patients with abuse, all significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels. Also, the left superior frontal gyrus had larger cortical thickness in male controls with abuse, compared to male controls without abuse, while it was smaller in male patients with abuse than in male patients with no abuse, results significant at $p < 0.05$ corrected for FWE.

4.2.2.1.1 Effect of physical and sexual abuse in childhood on brain structure

The presence of abuse was associated with no differences in grey matter volume and with a thickening of the right inferior parietal gyrus lateral orbitofrontal gyrus, irrespective of psychosis. The opposite emerged from the male sample, participants with history of abuse, irrespective of psychosis, showed smaller the right anterior cingulate, left paracentral lobule, left superior frontal gyrus, left medial frontal gyrus when compared with male participants without abuse exposure, but no differences in cortical thickness were found.

The findings corroborate a pattern of vulnerability for areas involved in higher order emotional and cognitive processes. Furthermore these brain regions are consistent with regions known to be abnormal in individuals with childhood abuse exposure in mixed-gender samples, and partially overlap what I have found in the entire sample (Teicher et al. 2006; Lim et al. 2014; McEwen et al. 2015). In the female group the exposure to childhood abuse was associated with a thickening of the frontal areas. High levels of

glucocorticoid and catecholamine have been associated with greater frontal areas, so this increase in thickness could be considered a result of the process to adapt to an adverse environment (Arnsten, 2015). Another explanation could focus on the effect of abuse on the development. Tomoda et al. (2011) found an increased grey matter volume in the right temporal gyrus associated with childhood maltreatment in a sample of healthy individuals. They proposed that exposure to early maltreatment may delay the normal development of sensitive brain regions, therefore greater brain areas found in individuals with abuse could be consequence of an incomplete maturation process. Interesting in the male sample there was an association between abuse and smaller paracentral lobule, a sensory-motor region, never linked with structural abnormalities and abuse before. Reduced grey matter volume was found in the post-central gyrus of individuals exposed to childhood abuse and was specifically associated with exposure to abuse at a very early age (Lim et al., 2014). Considering the topological proximity this may be the case for this area as well.

4.2.2.1.2 Interaction between psychosis and abuse exposure

Female cases with abuse showed a smaller cortical thickness than abused controls in the left pericalcarina cortex, right post-central gyrus, right superior frontal gyrus, right superior parietal gyrus, right cuneus and right inferior temporal gyrus. In males, left medial frontal gyrus volume was associated with greater grey matter volume in controls with childhood abuse history and smaller in cases exposed to childhood abuse. Similarly the left superior frontal gyrus showed a different effect in male cases and controls with male controls displaying greater cortical thickness than male case.

Most of these regions are heteromodal and involved in high order functions, with the exception of the pericalcarina cortex, a primary visual cortex (Klein, Paradis, Poline, Kosslyn, & Le Bihan, 2000). An association between trauma exposure and structural abnormalities in areas that process visual stimuli has exclusively been found in women (Tomoda et al., 2012). This may underline a particular vulnerability present in females.

4.2.2.2 Gender differences in brain structure in patients with and without a history of physical and sexual childhood abuse

There were no grey matter volume differences between female cases with and without history of abuse, whereas female cases with abuse showed a thinning of the latero occipital gyrus in comparison with female cases without abuse exposure, significant at $p < 0.05$ after FWE correction. Male patients showed

smaller grey matter volume in the inferior frontal gyrus, the left anterior cingulate and right post-central gyrus while there were no differences in the cortical thickness between male cases with and without abuse exposure, significant at $p < 0.05$ after FWE correction.

Male and female cases with history of abuse showed differences in primary sensory cortices, particularly the post-central gyrus (sensory motor region) and the left latero occipital cortex (sensory visual stimuli). Structural abnormalities in primary sensory cortices has been thought to be the consequence of abuse occurring at a very early age, as these areas complete their development during childhood (Tomoda et al. 2012; Lim et al. 2014). Interestingly, females showed an alteration in an area related to the processing of visual stimuli, confirming a similar association found when exploring the effect of abuse in females in my study and previously reported from another study on a female sample (Tomoda et al., 2012).

4.2.2.3 Gender differences in brain structure in patients with and without a history of physical and sexual childhood abuse

Among female controls a history of childhood abuse was associated with a larger grey matter volume in the left medial frontal gyrus, significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels, and a thicker left lingual gyrus, significant at $p < 0.05$ FWE. Male controls with abuse, when compared with male controls without abuse, showed a reduction in the grey matter volume of the middle frontal gyrus, right superior temporal gyrus, and right middle temporal gyrus, and larger grey matter volume of the middle frontal gyrus, all significant at $p < 0.001$ uncorrected for FWE with a cluster size of

100 voxels. There were no differences in cortical thickness between male controls with and without abuse exposure in childhood.

Again in the female sample there is an association between abuse exposure and an area involved in processing visual stimuli, the lingual gyrus has been already reported in literature as smaller in a young sample of females with no co-occurring psychiatric conditions exposed to trauma (Tomoda et al. 2012). It has been proposed that abuse can impact on the development of the brain delaying the maturation of this specific areas (Tomoda et al., 2011). As the participants in my study were older than those in Tomoda et al. (2012) (26.9 yrs. vs. 21.7 yrs.), the samples in the two studies could be at two different stages of their maturational processes. Both male and female showed and greater grey matter volume in the frontal, middle and medial gyrus respectively, in association with abuse. These areas are known to be involved in working memory and integration of other sensory modalities (Edmiston et al. 2011; De Brito et al. 2013; Philip et al. 2015). The concurrent stimulation of glucocorticoids and catecholamines can strengthen some neuronal circuitry in order to respond to the exposure to abuse and has been associated with increased volume in the frontal regions (Arnsten, 2015). This mechanism can be responsible for the increased of the brain areas I found in male and female controls exposed to abuse.

4.2.2.4 Overview of the gender differences on the effect of childhood abuse on brain structure

In line with hypothesis 3 the alterations in the brain structure associated with history of childhood abuse were different in cases and controls. The alterations in the brain structure associated with childhood abuse in male and female participants corroborate a configuration of vulnerability to childhood abuse for areas involved in higher order emotional and cognitive processes, in line with what I have found in the entire

sample, and with well replicated findings in the literature (Teicher et al. 2006; Lim et al. 2014; McEwen et al. 2015). Given the sample size, this analysis should be considered exploratory. Nonetheless, an interesting pattern has emerged, possibly resulting from different biological mechanisms in the two genders.

Men and women are exposed to a different hormonal environment throughout their lifespan. This has consequences on the structure of the brain, with a well defined sexual dimorphism of the adult brain; women are characterised by larger volumes, relative to cerebrum size, particularly in frontal and medial paralimbic cortices (Goldstein et al., 2001). Furthermore, women have higher neuronal density, number of gyri and an overall more complex brain surface than men, especially in the frontal regions (Lüders et al. 2002; Ruigrok et al. 2014). Finally, oestrogens are thought to moderate the effect of the main stress hormones (i.e. glucocorticoids and catecholamine) on neuronal architecture. Indeed they have been shown to modulate the neuronal cycle and to influence the magnitude of cortisol secretion (i.e. higher in the luteal phase) (Bale, 2015). In all the comparisons I produced (i.e. the effect of the abuse irrespective of psychosis, the interaction between abuse and psychosis, the assessment of cases and controls with and without trauma separately in the two genders), male structural abnormalities associated with childhood abuse were typically located in the anterior part of both hemispheres. Furthermore, it is noteworthy that the structural abnormalities were detected mainly through evaluation of the grey matter volume. As grey matter volume is more dependent on the variation of cortical surface than thickness, the effect reported may be the expression of differences in this component (i.e. the alterations could result from changes in cortical surface rather than thickness) . This is supported by the relative lack of findings in cortical thickness (Schultz et al. 2010; Sprooten et al. 2013). On the other hand, structural abnormalities in women were prevalently associated with variations in cortical thickness. The higher neuronal density and higher level of gyrification in the female cortex may make it difficult to identify grey matter volume

differences, whereas the finer resolution provided by the cortical thickness may prove more appropriate (Schultz et al. 2010; Sprooten et al. 2013).

Quite remarkably there was a consistent association of increased thickness in the frontal areas when the effect of abuse was accounted for and when controls with and without abuse were compared. On the contrary cases with abuse showed a thinner brain regions than not-exposed cases. This may signal that widespread structural changes are induced by the exposure to abuse in childhood, and the adjustment is really different between those who would not develop any psychopathology and those who would.

Both men and women showed changes in areas involved in the elaboration of sensory stimuli. However, in men these were in areas related to motor stimuli and in women to visual stimuli. It has been thought that alterations in sensory cortices subserve adaptive mechanisms that protect the child by sensory gating the abusive experience (Teicher et al. 2006; Tomoda et al. 2009; Tomoda et al. 2012; Lim et al. 2014). As these regions complete their development quite early, with no major architectural changes across the rest of the lifespan, it can be speculated that the abuse needs to have happened at a very early age to impact on them. This distinct pattern of changes, on the visual cortices among women and in the motor cortices among men, may signal a different level of vulnerability at early developmental stages between the sexes.

4.2.3 Effect of psychosis on the brain structure

A complex pattern of brain alterations was found when comparing cases and controls, irrespective of abuse exposure. Indeed, abnormalities were found in the frontal, temporal, parietal lobes as well as in the cerebellum. Cases had smaller grey matter volume in the right inferior temporal gyrus and right cerebellum, significant at $p < 0.05$ after FWE correction and in the left cerebellum, significant at $p = 0.055$ after FWE correction than controls. In terms of cortical thickness, the right supra marginal gyrus was thinner in cases than controls and the right rostral middle frontal gyrus was thicker in cases than controls, both at $p = 0.07$ after FWE correction.

4.2.3.1 Brain structure and psychosis, entire sample

I found that the superior temporal gyrus and the right and left cerebellum were smaller in patients with psychosis. The superior temporal gyrus is a complex, neocortical region encompassing unimodal auditory as well as heteromodal neurons. It is highly connected with other heteromodal regions (e.g. dorsolateral prefrontal cortex) to master complex activities such as focusing attention, activating working memory and exercising language (Pearlson 1997). Abnormalities in this area are a well-replicated finding in individuals with psychosis, both drug naïve and after prolonged treatment (Fornito et al. 2009; Fusar-Poli et al. 2012a; Fusar-Poli et al. 2012b). Furthermore, a smaller superior temporal gyrus has been associated with the occurrence of hallucinations in FEP, with more severe negative symptoms and with an overall poorer outcome at 5 years (van Haren et al. 2011; Fusar-Poli et al. 2012a). As ethnicity has been shown to play a role in the brain abnormalities associated with of psychosis, it is interesting to note that reductions

in the right superior temporal gyrus have been reported in patients of different ethnic origin, such as Japanese and Caucasian individuals (Gong et al. 2015). This may point to the smaller superior temporal gyrus as one of the most stable features of the illness across individuals of different ethnic origin.

A reduction in grey matter volume in the cerebellum has also been previously reported in first episode individuals as well as in patients with chronic schizophrenia (Fornito et al. 2009; Fusar-Poli et al. 2012a; Sheffield et al. 2013). Abnormal cerebellar structure has been associated with more frequent and more severe negative symptoms and with the misinterpretation of the environment, which is one of the prominent features of psychosis (Andreasen and Pierson 2008; Zhang et al. 2015). An impaired cerebellum would indeed integrate information more slowly, inefficiently and erratically, and therefore not perform its role as detector of logical errors. This would lead to alterations in cognitive performance (i.e. cognitive dysmetria) that over time would contribute to the formation of delusions (Andreasen and Pierson 2008). Somewhat surprisingly I did not find differences in the insula between cases and controls, a results often found in FEP (Fornito et al. 2009; Fusar-Poli et al. 2012a). It is interesting to note that I found this alteration associated with childhood abuse exposure. One interpretation could be that the smaller volume in the insula in FEP is the result of the combined effect of abuse and psychosis, rather than a distinctive feature of psychosis. Without accounting for the presence of abuse, which is rarely reported in FEP studies and yet relatively more prevalent in these individuals, alterations in this region could be easily attributed to psychosis alone. Furthermore, alterations in the insula are reported prominently by studies measuring the grey matter density, instead of grey matter volume (Fornito et al. 2009). As the techniques used to evaluate grey matter volume are more sensitive to the heterogeneity in brain morphology than those used to measure grey matter density, the alterations reported in literature may reflect more morphological variance than a true reduction in grey matter (Fornito et al. 2009).

I also found that patients with psychosis had a thinning of the right supra marginal gyrus. This has been previously found in individuals with schizophrenia (Schultz et al. 2010b; Goghari et al. 2011). Since the supra marginal gyrus has been reported to be active in tasks with high load of non-verbal component intelligence, its abnormality may explain the cognitive impairment reported in affective and non-affective psychoses (Bora et al. 2010; Bohlken et al. 2015; Bora and Pantelis 2015). Studies in FEP individuals have produced contradicting results depending on duration of illness, with some showing a reduction in the supra marginal gyrus in cases when compared to controls, while others, including the largest FEP sample to date, and others failing to report any significant difference in this area (Narr et al. 2005; Schultz et al. 2010a; Sprooten et al. 2013; Xiao et al. 2015). These discrepancies could be reconciled in light of illness length. As a longer duration of psychosis is associated with greater reduction of thickness, the small effect I have found in this area may be the consequence of the short duration of illness of my sample, as patients were recruited within three months of their presentation to psychiatric services (Narr et al. 2005; Schultz et al. 2010a; Sprooten et al. 2013; Xiao et al. 2015).

I found that the right rostral middle frontal gyrus is thicker in individuals with psychosis when compared with healthy controls. The right rostral middle frontal gyrus is one of the components of a neuronal network comprising other heteromodal association areas (e.g. supramarginal gyrus or superior-temporal gyrus) and responsible for the integration of multisensory input and for planning and evaluating behaviours (Buchanan et al. 2004). Alterations in this brain region are thought to be important in generating the core symptoms of psychosis (e.g. disorganization and distortion of reality) and have been associated with lower premorbid IQ (Pearlson et al. 1996; Gutiérrez-Galve et al. 2010). Abnormalities of the right middle frontal gyrus are consistently reported in individuals with chronic schizophrenia and less so at the beginning of the illness (Haren et al. 2008; Schultz et al. 2010b). Schultz et al. (2010a) have highlighted that the right rostral middle frontal gyrus showed the smaller effect size among the regions they found to be thinner in FEP compared with healthy controls. Furthermore Narr et al. (2005) found no

difference in this region between patients with psychosis and controls. The finding of the thickening of this area could be related to short illness duration. Indeed, it is thicker brain regions have been reported in individuals recently diagnosed with affective or non affective psychosis, and this is thought to be a compensatory mechanism present at the beginning of the illness, which may disappear with time (Schultz et al. 2010b; Xiao et al. 2015). The thinning of these regions, the right rostral middle frontal gyrus and the right middle frontal gyrus, is more consistently seen with the progression of the illness, but less so at the onset of psychosis (Schultz et al. 2010b; Xiao et al. 2015). It is possible that the thinning reflects an effect of type and length of medication exposure on the cortical structure (Haren et al. 2008; Schultz et al. 2010b; Ansell et al. 2014). For example, use of first and second generation antipsychotics has been found to correlate with changes in cortical structure, with a complex pattern of increase and decrease of cortical thickness (Ansell et al. 2014). Remarkably, a 8 week long treatment with second generation antipsychotics has been shown to increase the thickness of the right middle-frontal gyrus (Goghari et al. 2013). Also, studies on FEP include a wide range of participants in terms of illness duration and consequently drug exposure, from groups of medication naïve individuals, to samples with a longer history of illness and treatment as long as 4 years (Narr et al. 2005; Schultz et al. 2010a; Sprooten et al. 2013; Ansell et al. 2014; Xiao et al. 2015). This high level of variability may play a part in explaining discrepancies across studies, as those that included patients with a shorter duration of illness tend to show smaller effects or even increased cortical thickness where studies of FEP with longer medication exposure showed a reduction (Haren et al. 2008; Narr et al. 2005; Schultz et al. 2010a; Schultz et al. 2010b; Sprooten et al. 2013; Xiao et al. 2015). Thus, it is possible that the relatively short duration of illness and treatment length in my sample, 12 weeks on average, may help explain the small effect I found in these areas.

Another reason that could explain why differences failed to reach significance after correction for multiple comparisons could be the composition of the sample. FEP studies tend to encompass

predominantly male patients with the only exception of Xiao et al (2015) (Bora, Fornito, Yücel, & Pantelis, 2012). There is a well-defined sexual dimorphism of the adult brain, with women are characterised higher neuronal density, number of gyri and an overall more complex brain surface than men. Furthermore, they show larger volumes, relative to cerebrum size, particularly in frontal and medial paralimbic cortices (Goldstein et al. 2001; Lüders et al. 2002; Ruigrok et al. 2014). Psychosis is associated with small effect sizes in females, this tends to reduce the probability of reporting significant results in mixed-gender samples with a high number of female patients (Bora et al., 2012). Indeed, exploring abnormalities associated with psychosis in men and women separately, I have found that men showed grey matter volume changes in brain frontal areas compared to women and thinner cortical regions in association with psychosis than women.

4.2.3.2 Gender differences on brain structure in individuals with psychosis

Female patients, irrespective of the history of abuse, showed a smaller grey matter volume of the right cerebellum and left cerebellum than controls, all significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels. With regard to cortical thickness, female FEP, when compared to healthy controls, showed a thinning of the anterior cingulate significant at $p < 0.06$ after FWE correction. Male cases had smaller grey matter volume in the left middle frontal gyrus when compared with healthy controls, significant at $p < 0.001$ uncorrected for FWE with a cluster size of 100 voxels.

Similar to the cerebellar abnormalities discussed above, the reduction of grey matter volume in the left middle frontal gyrus, part of the dorsolateral prefrontal cortex, is a well-replicated finding in studies with mixed-gender FEP samples (Fornito et al. 2009; Fusar-Poli et al. 2012a). The frontal localisation of the

grey matter alterations in men and a more posterior localisation in women is consistent with a recent meta-analysis confirming that the frontal areas of the brain are more likely to be abnormal in male than female patients with schizophrenia (Bora et al., 2012). This difference may be a consequence of the different hormonal milieu in men and women during development, as discussed above. Interestingly, men with and without psychosis showed no significant differences in cortical thickness. Thus this divergent abnormalities (i.e. thinning in female whereas no difference in male patients) may explain the lack of statistical significance in the entire sample analysis after correction for multiple comparisons.

4.3. HPA axis activity and childhood abuse

I investigated the impact of childhood abuse and psychosis on the HPA axis activity focusing on two different aspects of its functioning separately. I first looked at alterations in the basal production of cortisol exploring the cortisol levels during the day to evaluate the presence of either hyper or hypo cortisolism in association with abuse exposure or psychosis, and then I studied the HPA axis capability of augmenting the hormone concentration in response to physiological stressor such as the awakening. Following the normal circadian rhythm, cortisol levels increase in the first 15-30 minutes after waking up and then decrease again within 60 minutes after waking (Miller, Chen, & Zhou, 2007). This spontaneous change, comparable to the activation required by the exposure to a medium stressor, has been consistently used to have information about the reactivity of the HPA axis and has been described as highly intraindividually stable (Dickerson and Kemeny, 2004). I investigated the cortisol awakening response by looking at both the total cortisol production in the first hour after waking (Cortisol Awakening Response with respect to the ground) and in the variation of the cortisol concentration from the cortisol levels at 0 minutes after waking (Cortisol Awakening Response with respect to the increase). I evaluated these cortisol measures across the different levels of abuse exposure (i.e. no abuse, mild abuse, moderate abuse and severe abuse) in the sample of individuals with and without psychosis to explore the reactivity of the HPA. I will discuss the results of the different measures of the HPA activity following the above order.

4.3.1 Cortisol levels during the day and abuse exposure in individuals with and without psychosis

I explored the difference in cortisol levels during the day across the different levels of abuse exposure (i.e. no abuse, mild abuse, moderate abuse and severe abuse) with a two-way ANOVA design, in the entire sample as well as in men and women separately. In the current study, it was not possible to neither differentiate cases and control on the bases of their overall level of cortisol during the day nor infer about their exposure to abuse during childhood. This is the biggest sample so far to have investigated possible alterations in basal cortisol production during the day in cases at first episode of psychosis and controls with and without history of abuse and these findings can help clarify the conflicting evidence from previous literature.

4.3.1.1 Cortisol levels during the day and abuse

Only three studies have so far investigated the relationship between basal cortisol production during the day and childhood abuse in healthy people, reporting conflicting results (Tarullo & Gunnar, 2006). This may explain why I found no differences in cortisol levels during the day in cases and controls with and without history of childhood abuse, contradicting hypotheses 1, 2 and 3. Gonzalez et al. (2009) found higher cortisol concentration in individuals exposed to trauma when compared with not exposed. In contrast, (Vegt, Ende, Huizink, Verhulst, & Tiemeier, 2010) reported no difference in cortisol levels during the day between adoptees with and without history of severe abuse. The third study (Brewer-smyth and Burgess (2008)), did not focus on diurnal cortisol levels but rather on the cortisol diurnal variation

and reported a smaller variation in cortisol levels between morning and afternoon in trauma positive participants when compared with healthy controls. The generalizability of the results from Brewer-smyth and Burgess (2008) and Gonzalez et al. (2009) is reduced as their samples were constituted only by female individuals, with Gonzalez using a very specific sample of women between 2 and 6 months postpartum. Furthermore, the definition of trauma differs across studies as one study only considered sexual abuse (Brewer-smyth and Burgess 2008) and the other a combination of parental loss and childhood maltreatment (Gonzalez et al. 2009).

The picture appears clearer when looking at psychiatric patients with history of abuse in childhood, as there are more studies and reviews in these individuals. Studies consistently show that depressed people with exposure to childhood abuse have higher basal cortisol level than controls, while the combination of abuse exposure and Post Traumatic Stress Disorder is associated with low basal cortisol levels (Tarullo and Gunnar 2006; McCormick and Mathews 2007; Strüber et al. 2014). So far, there are no studies looking at the effect of abuse on diurnal cortisol levels in psychosis.

A recent meta-analysis on the effect of chronic stress on HPA axis activity finds that in adults reporting exposure to physical threats or traumatic stressors in childhood the basal cortisol production tends to be comparable or lower than in controls (Miller et al. 2007). These findings support the presence of a reduction of the basal cortisol level compared with the high basal levels usually associated to children or adolescents with history of abuse exposure (Miller et al., 2007). The only longitudinal research on the effect of abuse on the stress response in people with history of non clinical depression and anxiety so far shows similar findings to the cross sectional studies (Trickett, Noll, Susman, Shenk, & Putnam, 2010). Individuals with history of abuse display a significant reduction in basal cortisol production from childhood to adulthood, their basal cortisol level shift from levels significantly higher than not-exposed controls to similar basal cortisol levels (Trickett et al., 2010). Unfortunately the participants in this study

were only female reducing the generalizability of these findings. My study investigated the largest mixed-gender sample and the findings can help understand also possible effect of gender in the relation between abuse and basal cortisol levels in adulthood. My results show evidence of a non-augmented basal cortisol production in individuals exposed to abuse in childhood, as individuals reporting abuse have similar cortisol levels during the day than not-exposed participants. The cross-sectional design of this study thwarts to draw conclusion on the variation of cortisol basal level from the time of abuse to adulthood. Nonetheless it is suggestive that previous studies in adult individuals with history of childhood abuse consistently show normal/low level of basal HPA axis activity in contrast with the well-established higher production which characterises abused children or adolescents (Strüber et al., 2014). This would suggest the ability of the HPA axis to change its activation pattern over time; it remains unclear whether this is an adaptive change to adjust to the environment or a sign of dysfunctional activity consequence of an altered development.

4.3.1.2 Cortisol levels during the day and psychosis

In my sample, patients with psychosis and healthy controls had similar levels of cortisol during the day. High basal level of cortisol, either in the blood or in the saliva, has been inconsistently found in FEP. Studies from Ryan et al. in (2004), Walsh et al. (2005), Spelman et al. (2007) and Kale et al. (2010) show increased basal level of circulating cortisol while Strous et al. (2004), Garner et al. (2011), Garcia-Rizo et al. (2012) and Van Venrooij et al. (2012) found no difference between FEP and healthy controls. Likewise two studies collecting salivary sample, as it is in my case, reported higher cortisol levels in

patients while another did not find any effect (Gunduz-Bruce et al. 2007; Hempel et al. 2010; Mondelli et al. 2010²⁰).

Looking at the different lengths of antipsychotic treatment across participants can help to better understand these findings. Indeed higher basal cortisol is evident in patients with no or minimal exposure to antipsychotic treatment (i.e. maximum three weeks), while studies whose participants were treated for longer periods fail to find any difference between cases and controls; this is true for both hematic and salivary cortisol samples (Ryan et al. 2004; Walsh et al. 2005; Gunduz-Bruce et al. 2007; Spelman et al. 2007; Mondelli et al. 2010 and Kale et al. 2010). Indeed, first and especially second-generation antipsychotics seem to reduce the basal HPA axis activity (Zhang et al. 2005; Borges et al. 2013; Mondelli et al. 2015). Moreover, treatment with second-generation antipsychotics can affect the cortisol concentration before, or independently from, the effect on psychotic symptoms thus normalising the cortisol when patients are still in an acute episode (Zhang et al. 2005; Borges et al. 2013). Therefore, the presence of wide range of treatment lengths and medication exposure can help explain these inconsistencies in literature as well as give context to my results (Borges et al. 2013; Karanikas et al. 2014). The overall majority of the participants in my study had been treated for more than three weeks and mostly with second-generation antipsychotics, which may explain the lack of significant difference in cortisol levels during the day between patients and controls, as a consequence of the normalising effect of medication on cortisol levels.

²⁰ The sample in my study comprises the sample used by Mondelli et al. 2010. That was a preliminary study conducted on a much smaller and selected sample than the one I used for this thesis.

4.3.2 Cortisol awakening response with respect to the ground and abuse exposure in individuals with and without psychosis

I explored the variation in cortisol awakening response with respect to ground across different levels of abuse exposure (i.e. no abuse, mild abuse, moderate abuse and severe abuse) with a two-way ANOVA design in the entire sample as well as in men and women separately. CARg was not significantly different between individuals with and without abuse exposure in the entire sample. Cases and controls showed significantly different CARg across the levels of abuse (i.e. no abuse, mild abuse, moderate abuse and severe abuse) highlighting an interaction between psychosis and abuse. The CARg was blunted for mild and moderate abuse and higher for severe abuse among controls and was blunted for severe abuse and higher for moderate abuse among cases. In the male sample I found significantly different CARg levels for the different severities of abuse. The CARg was blunted for male participants exposed to mild and severe abuse and higher for moderate abuse. Furthermore male cases and controls showed different CARg levels in response to abuse, signalling an interaction between abuse and psychosis. Male controls had blunted CARg in cases of mild, moderate and severe abuse; male cases had higher CARg for moderate abuse and blunted CARg for severe abuse. On the contrary female participants with and without history of abuse exposure had similar CARg. Interestingly female cases and controls had different CARg levels in presence of abuse exposure. Female controls had blunted CARg for mild and moderate abuse and higher CARg for severe abuse while female cases showed blunted CARg for mild, moderate and severe abuse. The distinct effects of abuse on CARg in men and women may suggest a divergent modulation by gender. The concentration of cortisol within the first hour after awakening is lower in cases than controls in the entire sample. Similarly when looking separately at male and female, both male and female participants with psychosis showed lower CARg than male and female healthy controls.

4.3.2.1 Cortisol awakening response with respect to the ground in individuals with and without history of childhood abuse

In the entire sample, CARg was different only at trend level across the individuals with different history of childhood abuse exposure (i.e. no abuse, mild, moderate, severe). In the male sample the exposure to abuse in childhood shows a differential effect on the CARg. In particular, individuals exposed to either mild or severe abuse have lower CARg levels than participants with no abuse; in contrast, those exposed to moderate abuse have higher level of CARg than those never exposed to trauma (figure 4.1).

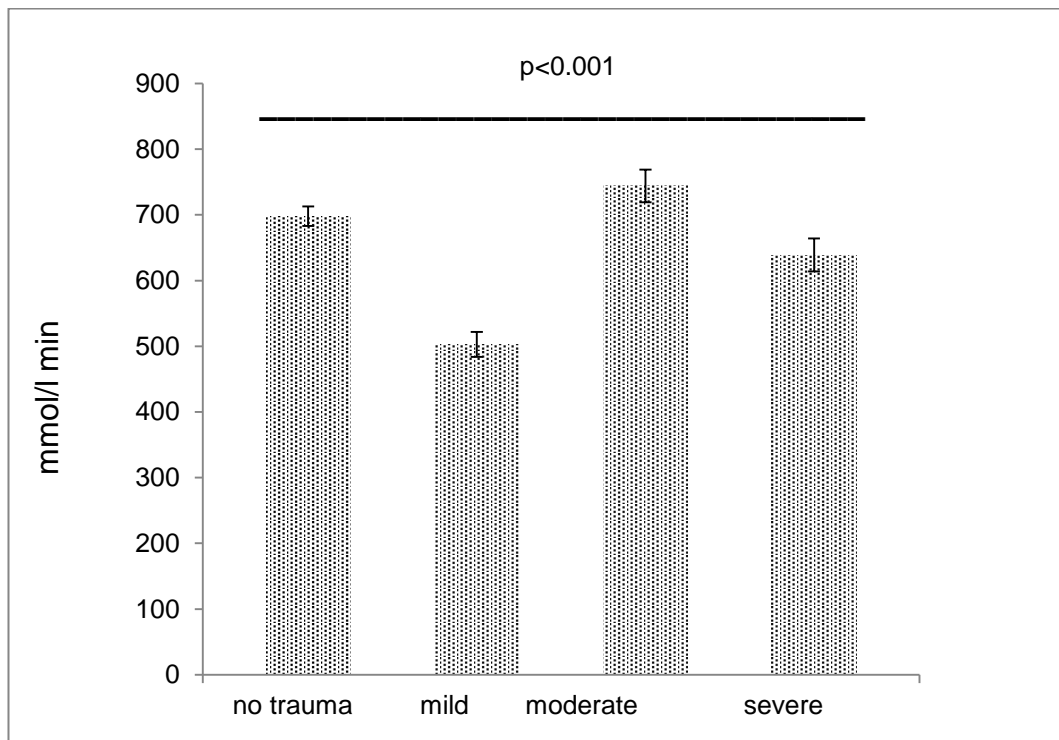


Figure 4.1: Cortisol Awakening Response with respect to the ground; main effect of abuse (male sample of patients and healthy controls together).

On the contrary there are no statistically significant variations of CARg across the levels of abuse in the female sample. The distinct effects of abuse on CARg in men and women indicate a divergent modulation

of the abuse on the HPA axis on the basis of gender, showing effect in male and no impact in female participants. This difference can help explain the findings when the sample is considered altogether, with one gender compensating the effect of the other.

The findings of blunted CARg in individuals exposed to mild or severe abuse and higher CARg in individuals exposed to moderate abuse in the male sample seem counterintuitive and difficult to interpret according to the current theories on the influence of trauma on the HPA axis activity. The more important hypotheses subordinate the cortisol production either to the severity or the length of the abuse exposure and neither of them seem able to explain my results (van der Vegt et al. 2009; Heim et al. 2010; Trickett et al. 2010). It has been proposed that the HPA axis reacts differently depending on the severity of the trauma exposure, with the more severe abusive experiences linked with a greater cortisol secretion (van der Vegt et al., 2009). In my study the more adverse experience (severe abuse) was associated with a CARg level similar to the less adverse experience (mild abuse), while the higher CARg level was associated with moderate abuse. On the other hand it is thought that the HPA axis reactivity depends on the length of the trauma exposure with longer period of abuse eliciting more attenuated cortisol production (Trickett et al., 2010). A similar association between the length of exposition to a hostile/stressful environment is for example present in a study on international adoptees (van der Vegt et al., 2009). This research showed that the later the participants were adopted, therefore the longer they were exposed to a hostile/stressful environment, the lower the production of cortisol and the CARg (van der Vegt et al., 2009). Indeed, in my male sample there was a significant difference in mean age of abuse across the varying levels of abuse severity: mild level of abuse occurred at a higher mean age (10.7 years), followed by severe (8.1 years) and then moderate abuse (6.6 years) (see Appendix B). Again this theory does not seem to be confirmed by my data, as the level of childhood abuse associated with older mean age of occurrence (mild abuse), which should have had the highest CARg, was the bluntest one instead. One explanation for these inconsistencies could be the wider range of abuse considered in my

study which uses an understudied category of abuse mild abuse; indeed in most studies the trauma severity is used as dichotomous variable (i.e. exposed to trauma vs not-exposed to trauma) or a continuous variable (Miller et al. 2007; Heim et al. 2010). One of the few studies that used the severity of trauma as a categorical variable, and the only methodologically comparable to mine, used two categories (i.e. moderate and severe) (van der Vegt et al., 2009). Interestingly they found higher CARg in individuals with exposure to moderate abuse and blunted CARg in people with exposure to severe abuse, as I did (van der Vegt et al., 2009). Furthermore in this study those with severe abuse exposure were those who stayed the longer in an hostile environment. Similarly in my case the individuals with severe abuse were significantly more likely than the individuals in the other groups to have experience co-occurrence of physical and sexual abuse, therefore a more adverse environment than the other groups of abuse (37% of male participants with severe abuse suffered both physical and sexual abuse vs only the 3.0% of the male individuals who suffered moderate abuse and 3.3% of the male individuals who suffered mild abuse, $\chi^2_{(2)} = 18.2$ $p < 0.001$)²¹ (van der Vegt et al. 2009). It is possible that beyond a certain level of intensity the exposure to childhood abuse ceases to elicit higher cortisol production; so the effect of abuse on the HPA axis may be increasingly stronger from mild to moderate abuse, prompting increasingly greater CARg, and then, for severe abuse, induce an lower cortisol concentration. A blunted CARg in response to severe abuse may promote adaptation and reduce the cost for the organism especially in terms of glucocorticoid toxicity (Fries et al. 2005). Interestingly it has been shown that resilient adolescent with history of maltreatment have lower cortisol response to stress than both non-resilient maltreatment and non-maltreated peers (Trickett et al., 2010). Thus the experience of profound abuse may induce a down regulation of the HPA axis leading to a reduce cortisol reactivity to stress. A similar reduction of the HPA axis activity (low levels of basal cortisol) has been reported in adults with depression and anxiety disorder who were severely abused as children (van der Vegt et al. 2009; Heim et al. 2010). Another explanation

²¹ The data on the age of abuse were present in 58% of the male sample.

could be that the adaptation to the environment is a function of an array of different elements (Miller et al. 2007). The response to abuse is indeed highly influenced by individual's characteristics in terms of biological milieu and social support; it is not unreasonable to think that the biological and social characteristics of male individuals could determine this pattern of results (Miller et al. 2007). This is the first study to explore the effect of abuse on a male sample; therefore it may be able to capture a pattern of CARg responses to childhood abuse otherwise undetectable in mx-gender study.

Higher CARg in individuals exposed to childhood abuse are thought to represent a protective mechanism through which the individual adapts to a stressful environment; they are quite commonly found close to the time of trauma exposure to change when time passes (Miller et al. 2007). Indeed HPA axis activity seem to change over time shifting from higher cortisol level in childhood/adolescence to lower in adulthood (Miller et al. 2007). One can only speculate about the reason and on the effects of childhood abuse exposure on the CARg. The reduction in CARg could represent an adaptation that occurs over time to the request of the environment, as a lower level of cortisol is thought to protect from the consequences of prolonged high levels of circulating glucocorticoids, thus minimizing the biological cost for the organism (Fries et al. 2005; Miller et al. 2007). Another explanation, which has been used mainly in the case of individuals who developed a mental illness after exposure to stress, is that, after a stimulus as overwhelming as abuse, the HPA axis exhausts its ability to produce cortisol later on in life (Lupien et al. 2009). The design of my study prevents me from drawing conclusions on whether the low CARg levels associated with mild and severe abuse result from an adaptation or an inability to produce cortisol. Nonetheless, as I will discuss in the next section, the cortisol awakening response with respect to increase (CARi) is similar in individuals with and without abuse, as well as in individuals with and without psychosis. As CARi evaluates the ability of the HPA axis to increase cortisol levels within the first hour after awakening, an exhaustion of the HPA axis would be coupled with a lower CARi, especially in individuals who would add to the history of childhood abuse a diagnosis of psychosis. On the contrary in

my sample it is not possible to distinguish between individuals with abuse and psychosis and healthy controls without history of abuse on the basis of the CARi values. This makes unlikely the presence of an exhaustion of the HPA axis.

In contradiction with hypothesis 1, there was no association between the CARg and exposure to history of childhood abuse. It is difficult to understand the relationship between childhood abuse and reactivity to stress based on the current literature, as this encompasses studies that used different methodologies to investigate HPA axis reactivity: awakening, psychological stressors and pharmacological challenge (Strüber et al., 2014). Most authors found that early adverse experiences reduce cortisol response to either psychological stress or dexamethasone/CRH administration²², indicating respectively a reduction in the HPA axis ability to increase cortisol in response to stimuli and an augmented negative feedback (Carpenter et al. 2007; Elzinga et al. 2008; Carpenter et al. 2009; Klaassens et al. 2009; Shenk et al. 2010; Carpenter et al. 2011). The only exception is one study which showed an increased reactivity of the HPA axis (Heim et al., 2000). The effect of gender in these studies has not been widely investigated, as all but two were constituted by a mixed-gender sample (Klaassens et al. 2009; Carpenter et al. 2011). Nonetheless the only one which investigated the effect of gender (Elzinga et al (2008)) found that the lower cortisol response to psychosocial stress in the sample was driven by the low reactivity to the task showed by men exposed to trauma. Focusing on the only studies that used CARg the evidence is still inconclusive, as there are reports showing adversity exposure having either increasing, decreasing or no effect on the HPA axis activity (Meinlschmidt and Heim 2005; Klaassens et al. 2009; Engert et al. 2011; Lu et al. 2013). Interestingly Klaassens et al. (2009) in a sample of healthy women with and without childhood abuse, aside the measurement of the CARg also stimulated the HPA axis pharmacologically

²² The dexamethasone/CRH is a well established laboratory procedure to elucidate the neuroendocrine feedback in the HPA axis. The administration of the Corticotropin-Relisin-Hormone (which stimulates the synthesis of the ACTH from the pituitary gland) is preceded by a pre-treatment with dexamethasone (a medication analogous to the cortisol). In healthy individuals the administration of dexamethasone prevent the increase of ACTH after CRH assumption (Heuser, Yassouridis, & Holsboer, 1994).

with a dex/CRH administration; they found that women exposed to childhood trauma showed a blunted cortisol response. This study highlighted that the mechanisms responsible for the cortisol increase in the CARg and the pharmacological challenge are different. This confirms that the response to dex/CRH administration relies on receptors in the paraventricular nucleus and the pituitary gland, whereas the awakening peak in cortisol concentration is the result of the activity of limbic and sovra-limbic structures (Pruessner et al. 2013). Results obtained with different methods are obviously difficult to compare.

All the studies mentioned so far did not differentiate levels of abuse, clustering together moderate and severe abuse, making the comparison with my results difficult. Indeed, there is only one study exploring the moderate and severe level of childhood abuse separately in a sample of international adoptees, using CARg (van der Vegt et al. 2009). The authors explored the effect of moderate and severe neglect and physical abuse separately and then combined them together, controlling for level of psychopathology. They found that, when compared to individuals with no abuse, there was a higher CARg in individuals reporting moderate trauma and a lower CARg in those with severe trauma. As the latter were the ones adopted later and therefore had the longest exposure to chronic stress, they also hypothesised that the low level of cortisol in the participants reporting severe abuse was the outcome of a more chronic exposure to traumatic experiences. Despite the inconsistencies and the wide range of methods present in the literature, it is evident that the exposure to adverse childhood experiences is associated with enhanced negative feedback of cortisol and that increased severity and chronicity of abuse impact incrementally on cortisol reactivity. Furthermore, when the role of gender has been investigated, the male participants were driving the finding of an alteration in cortisol concentration. In agreement with this finding, there is no effect of abuse in the only study using CARg in an entirely female sample (Klaassens et al., 2009). Despite methodological discrepancies these common elements are all consistent with my results of an effect of significant abuse on CARg levels in male but not in female participants.

In line with hypothesis 3 I found a different association between cortisol, gender and history of abuse exposure in cases as well as in controls. The lack of difference in the CARg profile in females with and without (any severity) of abuse exposure suggests that the adjustment to the exposure to this environmental stressor among females is obtained without a change in the CARg profile unlike males. Deviation from the normal HPA axis activity profile, even if to adjust to the environment, is usually associated with increased health risk (van der Vegt et al. 2009; Heim et al. 2010; Sapolsky 2015). Thus the profile showed by men exposed to abuse, even though it should be considered adaptive, is likely to be associated with a biological cost for the individuals. Therefore it would be interesting to know how this more effective adaptation (without deviating from the CARg levels present among not-abused controls) it is obtained in the female group. Unfortunately the mechanisms that can explain this difference are not clear. Numerous studies report that men and women differ in terms of free cortisol levels in response to stressors, with women having lower levels than men, and in the profile of the awakening response, with women having a delayed decrease of cortisol level when compared with men (Pruessner et al. 1997; Juster et al. 2015). Thus, the lack of statistically significant differences between women exposed and not exposed to abuse could be due to overall smaller amplitude in the range of hormone values, which in turn reduces the likelihood of detecting statistically significant differences between groups. A part from this potential explanation; it is worth to consider the role that oestrogens might play as these hormones have been shown to have a protective role against stress and stress related diseases throughout the lifespan (Gale and Gillespie 2001; Mozaffarian et al. 2015). Women are less inclined than men to develop illnesses in which stress and inflammation are aetiologically important or acknowledged risk factors, such as cardiovascular diseases and diabetes (Gale and Gillespie 2001; Mozaffarian et al. 2015). Oestrogen have also shown to modulate the effect of the cortisol response to stress as well as the perception of subjective stress, for example oestrogen increases the cortisol secretion and the subjective anxiety in response to stress during the lutein phase of the period (Duchesne & Pruessner, 2013). These hormones

may then activate other biological mechanisms in women to help the individual to adjust to the exposure to physical and sexual abuse without changing the levels of cortisol secretion when compared to non-exposed individuals. Another not mutually exclusive hypothesis would consider the role that social and environmental factors have in modelling the stress response. It is interesting that where men and women are affected by the same illnesses the way they describe it and the symptoms they report differ (Leening et al., 2014). Generally women report less intense symptoms (e.g. during an heart attack) than men, which incidentally increases their risk of underestimating the illness severity and receiving inappropriate treatment (Leening et al., 2014). The magnitude of the HPA axis response to stressor is modulated by the social and emotional characteristics of the stressors themselves (Miller et al., 2007). Tasks or situations with unpredictable elements (e.g. speaking in front of a public, be evaluated by strangers) elicit a bigger cortisol variation than pharmacological challenges (Dickerson and Kemeny 2004). Therefore it is not unreasonable to consider that also the characteristics related to the concept of masculinity and femininity may play a role in shaping the stress response as they can determine to some extent what is to be considered important to the self and to what a person is vulnerable to (Dickerson and Kemeny 2004; Dedovic et al. 2009). Interestingly women have a more intense cortisol response when psychosocial stimulation involves interpersonal elements, whereas men have more intense reaction in response to challenge (Dickerson & Kemeny, 2004). From this perspective an experience is able to stimulate the HPA axis depending on its nature and on the characteristics attached to it; ultimately to the degree to which it is perceived and responded to as a stressor (Martin H. Teicher et al., 2006). Therefore the way men and women are socialised, the diverse social milieu to which they are exposed to, the different ability to verbalise and seek form help, can partially explain the lack of effect of abuse on the CARg I found in women. The extremely high level of prevalence of abuse in the general population may make women more acutely aware of the issues related to physical and sexual abuse and its consequences reducing elements on uncontrollability linked with higher cortisol production (Dickerson and Kemeny 2004; Miller et al. 2007). On a more positive side this may give them the resources to effectively sought and attained

social support, which has been shown to reduce the biological impact of traumatic experiences (Miller et al., 2007).

Interaction between abuse exposure and Cortisol awakening response with respect to the ground

This is the first time the interaction between abuse and psychosis has been investigated. I found that different levels of abuse severity were related with different concentrations of CARg and these concentrations differed depending on the presence or absence of psychosis. Cases and controls exhibit a divergent effect of abuse on CARg levels: controls with history of mild and moderate abuse had lower CARg levels than controls without history of abuse exposure; in contrast, controls with severe childhood abuse had higher CARg than controls with no exposure. Interestingly the different CARg profile showed by cases and controls with abuse history, was partially in line with hypothesis 2 and 3. Cases with moderate childhood abuse show higher CARg levels than cases without abuse, cases with severe history of abuse exhibit lower CARg than those without abuse exposure, and finally cases with mild abuse had similar level of cortisol than cases without abuse exposure. When considering gender: male controls showed for all the levels of abuse severity lower CARg levels than controls without history of abuse, while male cases with moderate childhood abuse show higher CARg levels than male cases without abuse, and male cases with severe history of abuse exhibit lower CARg than those without abuse exposure. Female controls with history of mild and moderate abuse had lower CARg levels than those without history of abuse exposure, while female controls with severe childhood abuse had higher CARg than those with no exposure. On the other hand female cases with mild, moderate and severe abuse exposure have lower levels of cortisol than those without history of abuse in childhood.

The different patterns I observed between cases and controls exemplify the different ways in which HPA axis adapts to environmental stressors. The levels of CARg present in healthy individuals could be considered suggestive of a response to stress able to promote adaptation and reduce the consequences of too high or too low glucocorticoid stimulations (Robert M Sapolsky, 2015). Interestingly the individuals with psychosis and abuse exposure had different pattern of HPA axis response to stress in comparison with not-abused cases. Furthermore this pattern of activation is different from those showed by healthy controls with and without abuse. This may indicate that the challenge to react to childhood abuse determine a specific CARg profile, which does not seem to promote adaptation as these patients are characterized by worst symptoms severity, in the literature as well as in my sample.

Binding mineralocorticoid and glucocorticoid receptors, cortisol exerts widespread effect on the immune and central nervous system (Sandi & Haller, 2015). The window of positive effect is dramatically narrow so that either too high or too low concentrations can equally determine long term detrimental effects (Sandi & Haller, 2015). For example cortisol can directly reduce the dendritic length, of the synapses density, induce impairment of cellular turnover and neuronal apoptosis at both too high and low too concentrations (Arnsten 2015; Mcewen et al. 2015). Glucocorticoid can also promote the release of glutamate thus stimulating stress-induced remodelling of dendrites and synapses as well as excitatory toxicity in the hippocampus and in the frontal and prefrontal cortex leading to loss of neurons and changing in activation and length of neuronal circuitry (Arnsten 2015; Mcewen et al. 2015). Remarkably the areas that can be greatly affected by abnormal cortisol concentrations (e.g. hippocampus and the prefrontal cortex) are important in controlling the HPA axis activity (Heim et al., 2010).

Adjustment to the environment is an activity that requires the coordinated activation of all the individual's biological systems (Bale 2015; Chattarji et al. 2015). Individuals at risk to develop psychosis later on in life have shown abnormalities in the brain regions involved in the stress response (frontal areas and hippocampus) as well as the HPA axis (abnormal response to psychosocial stress) which can constitute a vulnerability in case of exposure to an adverse environment (Fusar-Poli et al. 2012b; Pruessner et al. 2013a). Indeed exposure to childhood abuse could induce a deterioration of both these systems already dysfunctional in psychosis (Mondelli et al. 2010b; Pruessner et al. 2013b; Arnsten 2015). This is even more important as these system can influence each other; cortisol abnormalities can promote an altered neuronal shape and an accelerated turn over in the brain region sensitive to glucocorticoid concentration while altered brain structure in the frontal and limbic areas can contribute to the cortisol dysregulation reducing even further the possibility to adapt to the environment (Teicher et al. 2003; McEwen 2007; Lupien et al. 2009). (Rao and Wu 2001; Bale 2015; Chattarji et al. 2015). These conjunct vulnerabilities can compromise higher order cognitive functions and ultimately the well-being of the individual and partially explain the different CARg profile I found individuals with psychosis and exposure to physical and sexual abuse in childhood (Teicher et al. 2003; McEwen 2007; Lupien et al. 2009).

4.3.2.2 Cortisol awakening response with respect to the ground and psychosis

My findings of lower CARg in cases than in controls is consistent with what reported in the literature (Mondelli et al. 2010; Pruessner et al. 2013). This is suggestive of an HPA axis dysfunction present in psychosis; the CARg is a proxy of the activation required by the HPA axis to respond to mild/medium stressors, thus a low rise in cortisol levels at awakening are likely to signal an impaired person's ability to respond to the demands of stressful situations (Dickerson and Kemeny, 2004; Pruessner et al., 2013).

Along with the regulation of the activity of the immunity system, the HPA axis is involved in modulation of the brain excitability in the hippocampus and the prefrontal cortex, having a pivotal role in the coordination of the behavioural and cognitive responses to external stimulations (Smith and Vale 2006; Pruessner et al. 2013b). Especially at central level, the delicate balance between the stimulation of the glucocorticoid receptors (i.e MR and GR) in different brain regions (i.e. hippocampus, frontal cortex, limbic system) hinges on the timely increase and decrease of cortisol concentrations (Sandi & Haller, 2015). As the relationship between cortisol levels and adaptive outcomes seems to follow an inverted u-shaped curve, too low or too high cortisol levels can promote changes at a neural cellular level and behaviours with non adaptive consequences (Sandi & Haller, 2015). Significantly an altered HPA axis activity has been linked with alterations in cognitive performances, memory retrieval, ineffective coping as well as abnormal brain structures. These cognitive alterations are present to a variable extent in stress related disorders and more importantly in psychosis (Goette et al. 2014; Ciufolini et al. 2014; Sandi and Haller 2015). The lower CARg along with findings showing a blunted cortisol response to psychosocial and psychological stressors in psychosis, could help to explain the cognitive and behavioural deficit characterising this illness (Ciufolini et al. 2014).

Pruessner et al (2013) reported an interaction between time of awakening and the CARg. They found that individuals waking later had lower cortisol production; as cases woke up later than controls, they proposed that this association could explain the differences in concentration between cases and controls. Furthermore they found that male cases had lower CARg than female cases; they proposed that this different CARg could reflect an overall more difficult relationship with parents in the male group, measured as parental bonding (M. Pruessner, Vracotas, et al., 2013). However, I found no significant differences in awakening time between cases and controls, and therefore I could rule out the possible confounding effect of time of awakening (8:04 a.m. among cases and 8:09 a.m. among controls, $t_{(309)} = 0.74$ $p = 0.7$). I found that both male and female cases had lower CARg than their healthy counterparts.

Furthermore when I compared male and female cases without history of abuse, I found no differences in CARg levels (-0.245 CARg male and -0.255 CARg female participants, $t(167) = 0.74$ $p = 0.7$)²³. The findings from Pruessner and colleagues could be explained in the context of the different impact of abuse depending on gender. This is consistent with my study where I found a significant effect of abuse in men but not in women, irrespective of the effect of psychosis.

4.3.3 Cortisol Awakening Response with respect to increase and abuse exposure in individuals with and without psychosis

I explored the differences in cortisol awakening response with respect to increase across the various levels of abuse exposure (i.e. no abuse, mild abuse, moderate abuse and severe abuse) with a two-way ANOVA design in the entire sample as well as in men and women separately. I found no effect of childhood abuse or psychosis on the Cortisol awakening response with respect to the increase (CARi) in the entire sample in contradiction with hypothesis 1 and 2. This signals that the capability of the HPA axis to increase the hormone concentration after awakening is the same in cases and controls, with and without history of abuse. Looking at the modulating effect of gender on the HPA axis, I found an effect of abuse on CARi in the female group but not in male. When compared with not abused individuals, female participants exposed to low and moderate abuse showed a reduced CARi and individuals reporting severe abuse had a higher CARi. This pattern was confirmed by a significant quadratic trend showing a decrease in cortisol production for low abuse (negative slope) and an increase for severe (positive slope).

²³ As specified in the methods (section 2.3.1) the analyses were conducted using z-scores to standardise the cortisol values obtained after the change of protocol of the study was modified, here I reported the z-scores.

4.3.3.1 Cortisol awakening response with respect to increase and abuse

In line with hypothesis 3 I found that female individuals exposed to abuse have different levels of CARi than those non-exposed, independently from being a case or a control. This is the first time CARi has been associated with abuse. The capability of the HPA axis to increase the cortisol production over time, the CARi, contributes to determine the cortisol concentration within the first hour after awakening along with the concentration of cortisol awakening (Pruessner et al. 2003; Chida and Steptoe 2009; Clow et al. 2010). Despite a close interrelation, the CARi and the CARg can change independently to one another (Chida and Steptoe 2009; Clow et al. 2010). The CARg is more dependent on the negative feed that regulates the HPA axis activity, while the CARi is greatly influenced by environment stimuli (e.g. light in the morning) and can adapt quickly and independently from the CARg to it (Chida and Steptoe 2009; Clow et al. 2010). The pattern present in individuals with abuse, showing higher or lower CARi levels in relation to the severity of the abuse exposure may be a compensative mechanism, which alternatively decreases or increases the hormone availability preventing hypo or hyper cortisolemia. The CARi has been tentatively associated with the current level of life stress experienced by the individuals; therefore, it cannot be ruled out that this result is influenced by the level of stress experienced by the participants (Chida and Steptoe 2009). In this case it would be remarkable that the level of stress experienced by the individuals at present would overlap with the severity of the physical and sexual experienced years before.

4.3.3.2 Cortisol awakening response with respect to increase and psychosis

I found no difference in CARi between cases and controls. There is only one study reporting a lower CARi in FEP when compared with controls. This study was conducted in a small sample (n=27 patients and 38 healthy controls) comprising patients with minimal (i.e. less than three weeks) exposure to antipsychotic treatment (Hempel et al. 2010). Another study reporting a difference in CARi between cases and controls is the one from one of my supervisors Mondelli et al., (2010). The participants from that study constitute a sub-sample of this present one. Participants in my sample had been exposed to antipsychotic on average for eight weeks, mostly with second-generation antipsychotics, and were older (mean age= 28.1 vs 22 years in Hempel's sample) than in the Hempel's sample. Although an effect of medication on normalizing the cortisol production cannot be ruled out, the size of my sample make it more representative of the population of interest, therefore more able to estimate the real effect of the illness (X. Y. Zhang et al., 2005). CARi, more than CARg, measures the ability of the HPA axis to increase the cortisol production at awakening; my results show that the potential for the HPA axis to increase cortisol production is the same in healthy individuals and in people with psychosis (J. C. Pruessner et al., 2003).

4.3.4. Correlation between age of abuse and cortisol levels

I investigated the presence of correlation between the age of abuse and the cortisol levels during the day, the CARg, and the CARi in cases and controls, in the entire sample, and in males and females separately. I found that the CARg positively correlated with age of abuse in the female sample, irrespective of the presence of psychosis. It is the first time a positive correlation between age of abuse and the level of CARg production has been reported in psychosis but a similar relationship has been previously reported in depression. The Corticotrophin Releasing Hormone (CRH) and the Adrenocorticotrophic Hormone

ACTH, two hormones that increase the concentration of cortisol, positively correlate with the age of abuse in patients with depression and healthy controls exposed to childhood maltreatment (Carpenter et al. 2004; Heim et al. 2008). Interestingly the positive correlation between age and cortisol concentration was present in patients as well as in controls exposed to adverse experiences (Carpenter et al. 2004; Heim et al. 2008). Similarly to my study the adverse experiences in Heim et al. (2008) was severe physical and sexual abuse. In line with these findings, I found the correlation in cases as well as in controls in the female sample, where the adaptation to the exposure to childhood abuse happened without changes in the CARg profile in exposed individuals compared with not-exposed individuals. This can lead to suggest that the HPA axis is sensible to the exposure to environment stressor (here childhood abuse) throughout the course of its maturation but reacts differently depending on the stage of the development when the exposure occurs. Furthermore in psychosis this correlation could be one of the mechanisms that, at least among female, promote adaptation to abuse with minimal changes in the HPA axis activity.

4.4 Brain structure, HPA axis activity and childhood abuse

I correlated the levels of cortisol during the day, CARg and CARi with the brain regions that were associated with abuse exposure. These were the areas showing a main effect of abuse in the entire sample (section 3.2.1.1), an interaction between abuse and psychosis in the entire sample (section 3.2.1.1), and different cortical thickness between cases with and without abuse (section 3.2.1.2). The cortisol levels during the day and the CARi correlated negatively with the thickness of the right medio orbitofrontal gyrus and lingual gyrus, the two brain regions which were thinner in individuals exposed to physical or sexual abuse in the entire sample. Furthermore, only among controls was there a negative correlation between cortisol levels during the day and the right cuneus, the latero orbitofrontal gyrus, the superior frontal gyrus and the interior parietal gyrus controls; 4 of the 6 regions associated with an interaction between abuse and psychosis. Among the 5 areas showing different thickness between cases with and without abuse, only the thickness of right medial orbitofrontal gyrus correlated negatively with the cortisol levels during the day and the CARi.

Only 3 studies have previously found a negative correlation between the structure of brain and cortisol levels, two in individuals with history of maltreatment and one in a twin study (Treadway et al. 2009; Kremen et al. 2010; Lu et al. 2013). Treadway et al. (2009) found a negative correlation between the level of cortisol during the day and grey matter volume in the rostral anterior cingulate in a sample of individuals with depression and history of early adversities and healthy controls. Similarly, Lu et al. (2013) in a sample of healthy individuals with and without history of childhood trauma, found an inverse correlation between CARg and grey matter volume in the right middle cingulate. Finally, Kremen et al. (2010) found a negative correlation between cortisol levels during the day and cortical thickness of the

left superior frontal gyrus, left rostral middle frontal gyrus and ventrolateral prefrontal regions, and right dorsolateral, superior frontal gyrus and medial orbitofrontal cortex in a sample of male middle-aged twins. Glucocorticoid receptors are highly expressed in the frontal areas, and the orbitofrontal cortex and the cingulate are directly involved in the inhibitory (GABAergic) tone of the hippocampus on the HPA axis activity (Sandi & Haller, 2015). Thus, the negative correlation between cortisol levels and frontal areas can be conceptualised as result of this modulatory activity on the HPA axis, in an attempt to balance the glucocorticoid levels and avoid hyper and hypo secretion (McEwen et al. 2015; Sandi and Haller 2015). The potentially negative effects of excessive concentration of corticosteroid on the brain could explain the negative direction of this correlation (Sandi & Haller, 2015).

Similarly, I found a negative correlation between the cortisol levels during the day (a indicator of long-term activity of the HPA axis) and the CARi (an indicator of short-term reactivity) with the right medio orbitofrontal gyrus and lingual gyrus, areas smaller in individuals exposed to childhood abuse. The negative correlation between cortisol levels during the day, CARi and the medio orbitofrontal cortex, which directly regulates the HPA activity through the activation of the paraventricular nucleus, can be interpreted along the line of a functional relationship with the HPA axis (Cohen et al., 2006). I found an abnormal patterns of HPA axis activity in cases as well as in controls with a history of abuse. My result of a thinning of this area in individuals with childhood history of abuse could be the consequence of these cortisol secretion patterns. The lingual gyrus is not regarded as a brain region that usually modulates cortisol levels, so this correlation is interesting and could help shed light on the mechanisms behind the effect of abuse of the brain. It is known that environmental factors can change the sensitivity of a brain region to the exposure of glucocorticoid (Strüber et al., 2014). The exposure to abuse in childhood could have increased the sensitivity of the lingual gyrus to cortisol stimulation and therefore reduced its thickness in individuals with history of abuse.

Interestingly I found a negative correlation between the cortisol levels during the day and the right cuneus, the latero orbitofrontal gyrus, the superior frontal gyrus and the inferior parietal gyrus controls only among controls. These are the areas showing interaction between abuse exposure and psychosis (i.e. these areas are thinner in cases with childhood abuse exposure and thicker in controls with history of abuse in childhood). They are all responsible for higher order emotional and cognitive processes and remain under development until late adolescence (Sowell et al., 2003). Even more importantly I found that these regions in healthy controls, who despite the exposure to physical and sexual abuse did not develop psychosis, have increased cortical thickness. Cortisol can increase as well as decrease dendritic concentration and synapsis density, and thus influence and sustain the tropism of these brain regions during their development. This could represent a resilience factor against the negative consequences of the exposure to childhood trauma. Indeed cases who unlike controls showed cortical thinning in these areas do not have the correlation between cortisol levels during the day and the thickness of these areas. This highlights even more the potential adaptive role of this relationship between cortisol and brain structure. As adaptation to stress is composed of biological and behavioural adjustments, these areas could, especially in healthy individuals, promote behavioural outputs that favour adjustment to the environment and influence (lower) cortisol production. This could determine a more bidirectional relationship between these regions and the HPA axis.

I found that not all the areas showing interaction between psychosis and abuse correlate with cortisol, indeed both in cases and in controls the post-central gyrus and the pre-central gyrus do not correlate with the cortisol levels during the day. These two regions are intrinsically different from the others as they are a primary motor and a primary somatosensory region (Sowell et al., 2003). The post-central gyrus and the pre-central gyrus do not have any regulatory function on the activity of the HPA axis and their tropism seems to be independent from the cortisol concentration. This could explain this lack of correlation. Furthermore, those areas complete their development years earlier than the other regions (Toga et al.,

2011). Therefore, cortisol has a relatively shorter time to impact on these areas. This could also signify that there are other mechanisms promoting their tropism, and they may play other roles in helping adaptation to childhood abuse. Unlike the CARg, neither the cortisol levels during the day nor the CARi differed between individuals with and without history of abuse in my study. Thus, it may seem counterintuitive that these measures of the HPA axis activity correlated with cortical thickness values. Environmental factors like childhood abuse can modify the expression and the activity of the glucocorticoid receptor, and therefore regions of the brain affected by abuse could express more sensitive receptors to cortisol, and thus be influenced by the hormone even in absence of a significantly greater concentration (Strüber et al., 2014).

The right medial orbitofrontal gyrus is the only area, of those smaller in cases with history of abuse exposure compared with not-exposed cases, to negatively correlate with the cortisol levels during the day and the CARi. Unlike the regions thinner in cases with history of childhood abuse, the medial orbitofrontal gyrus is the only one involved in the cortisol regulation therefore it could also suffer the structural consequences of its hyper concentration (Cohen et al., 2006). This underlines the regulatory role of this area over the cortisol production and the detrimental effect of too high cortisol concentration also among cases.

To conclude, in line with hypothesis 4 I have found an interrelation between cortisol level and the brain architecture not only in areas known to be rich in glucocorticoid receptors or involved in the regulation of the HPA axis. I have also found a negative correlation between areas showing interaction between abuse and psychosis only in individuals resilient to childhood abuse. First, this may imply that the architecture of some brain regions is influenced by the HPA axis activity and cortisol concentrations. Furthermore, the presence of a relationship between cortical thickness and cortisol levels only in resilient individuals may be an adaptive mechanism to childhood sexual and physical abuse which requires a finely organised

response of these different biological systems over time. This may suggest that the efficacy of adjustment to the environment, especially in extreme situations, may in part depend on the ability of specific brain regions and the HPA axis to coordinate a finely organised biological response.

4.5 Limitations

There are some limitations and methodological consideration that need to be taken into account and considered in the interpretation of the findings.

As psychosis and childhood abuse have relatively low incidence and prevalence, a prospective study to investigate how physical and sexual abuse increase the risk of psychosis and its biological mechanisms would be difficult for ethical and practical consideration. Therefore, the design of the study was cross-sectional and evaluated retrospectively the exposure to childhood abuse in individuals with a diagnosis of psychosis. This poses two important limitations.

First, causality cannot be inferred from the associations I found. Brain and HPA axis are flexible systems that constantly adapt and change in response to the environment. A cross-sectional evaluation cannot establish whether abnormalities in these systems represent the consequence of the abuse in childhood or later experiences or present circumstances. The same limitation applies in relation to childhood abuse, brain structure, HPA axis abnormalities and the presence of psychosis.

The second limitation concerns the reliability of the information on abuse exposure. Retrospective instruments have been criticized for the possibility to record unreliable and inaccurate information on traumatic memories that happened a long time ago, and that may be affected by normal process of alteration and forgetting (Wolkind and Coleman 1983; Harrison 2001). Although a certain amount of inaccuracy cannot be eliminated, the researchers collecting information on trauma exposure were provided with intensive training and consensus meetings to ensure the quality, accuracy and reliability of

assessments. Furthermore, the same interview as the one of this study was used in a sample of individuals with and without psychosis from South London with good levels of convergent validity with clinical case notes and patients' reports stable over a 7-year period (Fisher et al., 2011).

The recruitment of patients for this thesis took place across different psychiatric services in the South London and Maudsley NHS Trust. Due to some natural delay in approaching patients, it was very difficult to recruit individuals who were not already taking antipsychotic medications. Even though I did not find any significant difference in the total exposure to medication across patients with different histories of childhood abuse exposure (i.e. no abuse, mild, moderate, severe abuse), an effect of these drugs on the brain architecture as well as on the HPA axis functioning cannot be completely excluded.

During the recruitment process, individuals were excluded if they reported or had symptoms of psychosis, and included in the study if they were free of any psychopathology at present. This recruitment procedure did not assure the absence of psychiatric condition in the past (e.g. depression or anxiety disorders). The potential presence of psychiatric conditions in the past could have influenced the findings on the brain architecture and the HPA axis activity.

Exposure to early adverse experiences has often been associated with abnormal cognitive functions in adulthood. As the regions I have found to be related with history of physical and sexual abuse are crucial for higher cognitive functions, it would have been important to explore the relationship between abnormal cognition and these structural alterations, and potentially their role in mediating the effect of abuse over time. Unfortunately the dataset I used for this project did not include sufficient information on cognition to investigate this relationship.

Not all the individuals part of the wider study, in which my thesis was nested, accepted to undergo an MRI scan or collect the saliva samples required for the investigation of the HPA axis activity. This may have introduced a selection bias and therefore reduced the generalizability of the findings of the study.

There are a few limitations that intrinsically characterise the use of structural MRI. The spatial resolution provided by the structural MRI is unable to detect signals at a cellular level. The MRI signal can be identified from areas of a space scale of millimetres/sub-millimetres where different thousands of cells are comprised. Despite the fact that post-mortem studies have associated alterations detected with the use of structural MRI with neuronal abnormalities, the spatial resolution of this instrument prevent a clear distinction between alterations regarding neurons or any of the other cells present in the brain (e.g. astrocytes, microglia), thus it is not possible to indubitably attribute changes in grey matter volume and cortical thickness to neuronal alterations. The MRI signal is reconstructed into coherent images using mathematical algorithms and each of these algorithms depends on assumptions about the characteristics of the brain as well as of the signal itself. The presence of noise in the MRI signal may undermine the efficacy of the reconstruction algorithms. Furthermore, the analysis techniques are based on some properties of reconstructed images. Over the years there has been the collection of a large amount of normative data to guide the creation of standard robust algorithms to reconstruct the MRI signal and the definition of robust pipelines to analyse the neuroimaging data. Additionally findings obtained using these standard algorithms and pipelines have been validated with post-mortem studies. Nonetheless, it cannot be excluded that the anatomical accuracy of the reconstruction is limited by the noise of the MRI signal or inaccuracies present in the reconstruction algorithms. Similarly it cannot be excluded that the use of different analysis techniques would have determined different results or the location of the signal differences would have been placed in different brain areas.

Finally, although the participants completed information sheets during the saliva collection, the collection of saliva was unsupervised and it is therefore impossible to confirm if the saliva collection was performed at the designated time of the day. Since the concentration of cortisol in the blood as well as in the saliva varies physiologically throughout the day (e.g. higher in the morning and lower in the evening), collection time is crucial to accurately define the diurnal decline in salivary cortisol, and to characterise cortisol awakening response. Therefore incorrect report of saliva collection times could determine a blunter cortisol awakening response and lower levels of cortisol during the day, if the samples were collected later than the reported time. Unfortunately the strategies put in place to monitor the quality of cortisol data (e.g. completion of collection sheet, refrigeration of samples, determination of saliva concentration) cannot detect possible erroneous report of saliva collection time. In future research this could be addressed employing electronic collection devices where the participants can store the saliva samples. This device would be able to record the time when the saliva has been stored minimising the risk of incorrect records by the participants.

This study also has many important strengths.

The sample recruited for this study is one of the largest in the field (of both abuse and psychosis) Furthermore a distinct feature of the design is a relatively large group of healthy individuals exposed to childhood abuse, which allows the study of resilience to traumatic experiences. Additionally, this is one of the few studies to explicitly account for the presence of psychiatric illness when exploring the effect of abuse. Also the study is very homogenous in terms of abuse exposure as all the individuals reported history of physical and sexual abuse, this minimises the confounding effect of clustering together different types of abuse, often present in other studies in the field of abuse.

Finally I used a range of different measures to study the impact of abuse on the brain structure and on the HPA axis. Grey matter volume and cortical thickness measures have conveyed information on different spatial scales and on different determinants of brain structure, complementing each other and contributing to a more nuanced understanding of the brain architecture associated with abuse exposure. Similarly the cortisol levels during the day, the cortisol awakening response with respect to the ground and the cortisol awakening response with respect to the increase have shown different features of the HPA activity gathering information about the basal activity and the response to physiological stressors in individuals with childhood abuse exposure, which was never done before.

These characteristics of the design and the methodological choices may have helped to shed some light on the biological mechanisms in action in childhood abuse, an otherwise elusive topic

4.6 Conclusion

The biological mechanisms that increase vulnerability or confer protection against abuse remain subtle, as often different types of traumatic experiences are clustered together and samples examined do not usually include resilient individuals. My study makes a strong contribution to the current knowledge on the effects of childhood abuse on the brain architecture and on the HPA axis activity in psychosis as well as in the general population. Indeed, my sample of first episode psychosis patients and healthy individuals, with and without history of physical and sexual abuse in childhood, offers the rare opportunity to understand the impact of abuse exposure on resilient individuals. Furthermore, the distribution of abuse severity in the sample gives the possibility to study the mechanisms that are in action with abuse more clearly.

My results show that physical and sexual abuse has an impact on brain structure (i.e. grey matter volume and cortical thickness reductions in the frontal, temporal and limbic regions) but not on HPA axis activity when controlling for the presence of psychosis.

This study it is the first to show that abuse and psychosis interact in specific areas of the brain and on specific aspects of the HPA axis functioning. Remarkably, first episode psychosis patients and healthy controls exposed to childhood abuse show distinct patterns of brain alteration (increased grey matter volume and cortical thickness in controls and reduced in cases) and HPA axis activity (different pattern of cortisol awakening response with respect to ground in cases and controls).

Furthermore, my thesis also shows that childhood abuse has a different effect on the brain and on the HPA axis activity depending on gender. Female individuals show an effect of abuse on a number of brain areas, mostly related to alterations in cortical thickness, while men show an effect of abuse on a small number of regions, possibly related to changes in the cortical surface. Interestingly, the effect of abuse on these biological systems seems to be modulated by gender as the HPA axis activity was abnormal in male individuals exposed to abuse (altered levels of cortisol awakening response with respect to ground) but not in females.

Finally, my study showed a correlation between the HPA axis activity (cortisol levels during the day and cortisol awakening response with respect to increase) and the structure of brain areas sensitive to abuse exposure (cortical thickness). Furthermore, a correlation between the HPA axis activity (cortisol levels during the day) and some of the areas showing interaction between abuse and psychosis (cortical thickness) emerged in resilient individuals but not in cases exposed to childhood abuse.

4.6.1 Future directions

The findings from my study raise further questions, which I believe, are of great importance for future analyses.

In my future work, I would like first to investigate whether the alterations found in the brain architecture translate into abnormal connections between the regions interested. I would explore whether the network of structural correlations among the different brain regions would change as a consequence of abuse exposure. I would explore whether there are differences in the structural networks between individuals

exposed and not exposed to childhood abuse and then if the brain network associated with abuse is difference between cases and controls with history of abuse exposure.

I would also like to investigate whether the social support of these individuals can modulate the impact of childhood abuse on brain structure and HPA axis reactivity. I would explore whether differences in the network of social relationships can account for the different abnormalities in brain structure and HPA axis activity I have associated with abuse in cases and controls with childhood abuse exposure.

Furthermore, I would like to explore the relationship between genes and the vulnerability to the effect of childhood abuse. As cases and controls with history of exposure show different patterns of alteration these could be influenced by a different genotype and different expression of specific genes. As part of the wider study in which my thesis was nested, DNA and RNA sample were collected. I believe it would be of great value to explore the role of genes know to be implicated in stress response and psychosis, such as FKBP5, DISC 1 and BDNF, on the brain structure and HPA axis alterations associated with abuse exposure.

Finally, although not analysed in this thesis, the patients were followed-up as part of the original study at 3-months and 1-year. In a future project, it would be of interest to analyse the possibility of predicting clinical and functional outcomes in relation to the brain and HPA axis abnormalities found at baseline. Over this long period of time it would be interesting to assess the relationships between abuse exposure and treatment response, clinical outcome in particular remission, recovery and treatment resistance. It would also be important to analyse whether these features are stable across time and if they are influenced by the exposure to antipsychotic treatment.

APPENDIX A

Instruction sheet for saliva sample collection

Measuring your biological levels of Stress:

A step by step guide for the saliva collection

DATE OF SALIVA COLLECTION: _____

Name Initials _____

Saliva Code _____ EUGI ID: _____ GAP Barcode _____

Baseline ☐ 3 Months Follow up ☐ 12 Months Follow up ☐ Control ☐

Wake up (before 10 a.m.).

Immediately after waking up collect your saliva putting the Sorbette *under the tongue* and leaving it for 2 minutes, then put it back in the tube **marked 0**.

Write here the **EXACT TIME OF AWAKENING:** _____

Try to sit down and relax in the next hour. **YOU CANNOT BRUSH YOUR TEETH AND CANNOT HAVE ANYTHING TO EAT OR DRINK FOR THE NEXT HOUR.** If you need, you can drink water, but only immediately **AFTER** you have taken the sample.

15 minutes after waking up, collect your saliva using the **tube marked 15**.

- What time is it now? _____
- What were you doing before giving the sample? _____

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here: _____
- Did you have any difficult or tense situation, unpleasant thoughts or any kind of pain before taking this sample? If yes, please describe it here: _____

30 minutes after waking up, collect your saliva using the **tube marked 30**.

- What time is it now? _____
- What were you doing before giving the sample? _____

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here: _____
- Did you have any difficult or tense situation, unpleasant thought or any kind of pain before taking this sample? If yes, please describe it here: _____

60 minutes (1 hour) after waking up collect your saliva using the **tube marked 60**.

- What time is it now? _____
- What were you doing before giving the sample? _____

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here: _____
- Did you have any difficult or tense situation, unpleasant thought or any kind of pain before taking this sample? If yes, please describe it here: _____

******* You can now have breakfast and brush your teeth! *******

At 12, noon - before lunch collect your saliva using the **tube marked 12**.

You should not eat or drink anything, or do not brush your teeth in the 30 minutes before noon.

- What time is it now? _____
- What were you doing before giving the sample? _____

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here: _____
- Did you have any difficult or tense situation, unpleasant thought or any kind of pain before taking this sample? If yes, please describe it here: _____

At 8 pm - before dinner collect your saliva using the tube marked 8.

You should not eat or drink anything, or do not brush your teeth in the 30 minutes before 8pm.

- What time is it now? _____
- What were you doing before giving the sample? _____

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here: _____
- Did you have any difficult or tense situation, unpleasant thought or any kind of pain before taking this sample? If yes, please describe it here: _____

Store the tubes away from the heat and direct sunlight and put them into the fridge as soon as possible.

Please note name and time of any **medication taken today** (including the contraceptive pill):

Do you have any **medical problem**? If so, please list them here _____

If you are **female**: Please indicate the age of your first menstrual cycle: _____

And please indicate the date of the first day of your last menstrual cycle: _____

If you have any questions about any of these instructions please call our team,
0207 XXX XXXX or XXXXXXXXXXXX.

Collecting the saliva samples

1. Take the salivette marked with the appropriate number and carefully remove the lid (the part on the end with ridges on it).
2. Tip the cotton wool swab into the lid of the tube, then use this to place the swab in your mouth. **Do not touch the swab with your fingers.**
3. Gently chew the swab, repeatedly turning and moving it around in your mouth, for two minutes, so that it is saturated with saliva. This may seem longer than you expect, but the people in the laboratory need a lot of saliva for their analyses!
4. Take the swab out of your mouth with the help of the lid (so you are not touching it with your fingers) – it may be easier if you are looking in a mirror to do this. Tip the cotton bud back into the inner tube, again without touching the swab with your fingers.
5. Put the lid back on firmly.
6. Store the finished samples in the fridge.



APPENDIX B

Difference in age of abuse in the male sample

The model including age of abuse to explain the variation across the differed levels of childhood abuse (i.e. mild, moderate and severe abuse) in the male sample (81 individuals) was statistically significant ($F_{(2, 81)} = 5.11, p = 0.009$). The overall effect was driven by the age of abuse in the group with moderate abuse as shown by the post hoc tests with Bonferroni corrections (figure b1).

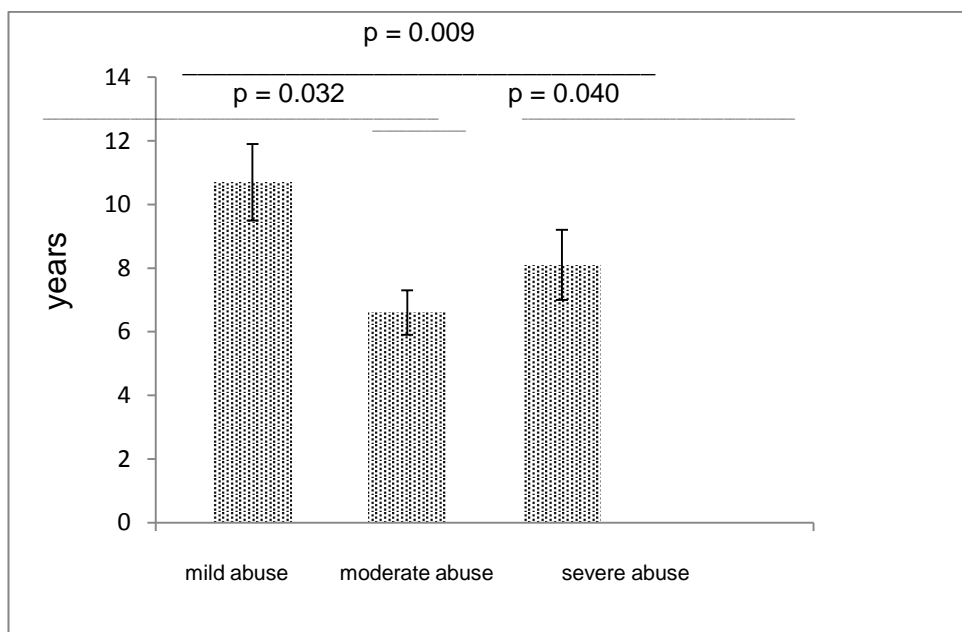


Figure b1: Difference in age of abuse in the male sample, error bars represent standard deviations

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